

Trapping the key intermediate in nucleophile-initiated Michael reactions

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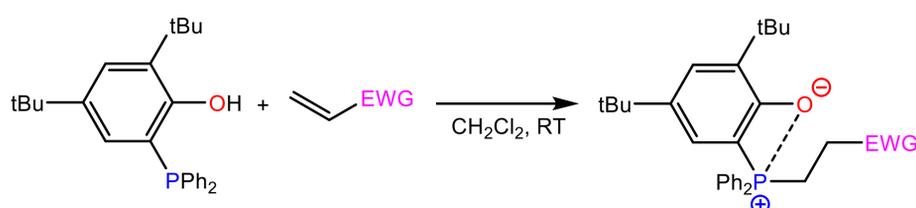
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Introduction

Nucleophilic catalysts are of high interest as alternatives to commonly used base catalysis in carba-, thia-, and oxa-Michael reactions. Catalysis starts with the reaction of the nucleophile with the Michael-acceptor, forming a zwitterionic species.¹ To gain a deeper understanding on the factors governing this initial step of catalysis, we study the reaction of ortho-hydroxy substituted phosphines with Michael-acceptors, whereby stable, isolable zwitterionic species are generated.

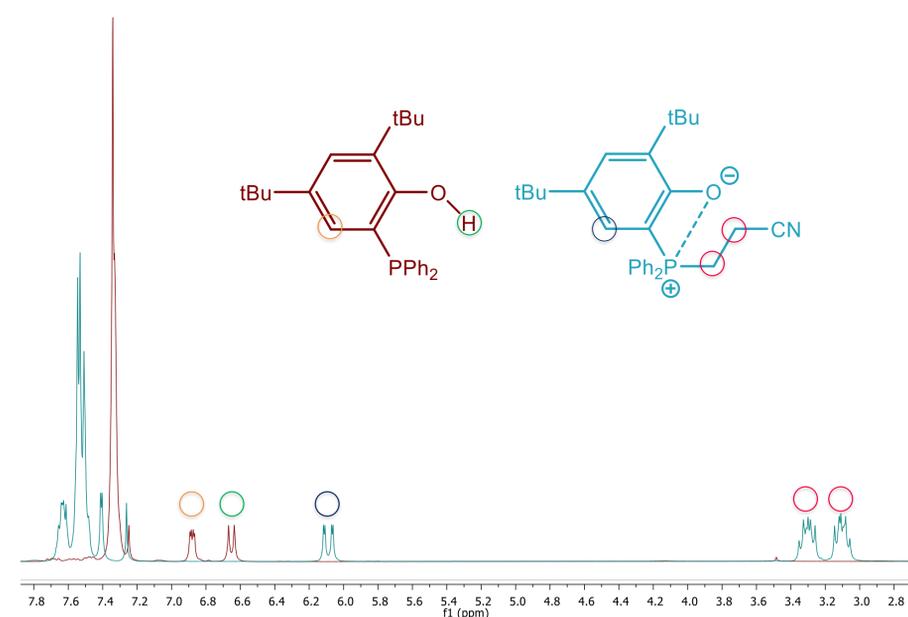
Synthesis



Preparation of zwitterions from ortho-hydroxy substituted phosphine

The synthesis of zwitterions is quite readily achieved by combining the phosphine and the Michael-acceptor in a 1:1 molar ratio in CH₂Cl₂ and stirring at room temperature, leading to complete conversion towards the zwitterion within 24 h. This reaction has been performed for a wide array of Michael-acceptors, including methyl vinyl sulfone, methyl vinyl ketone, various acrylates and acrylamide. Interestingly, acrylonitrile, a very reactive Michael-acceptor according to its electrophilicity parameter,² reacts much slower than for example acrylamide, which is known to be a rather poor Michael-acceptor.

Characterization



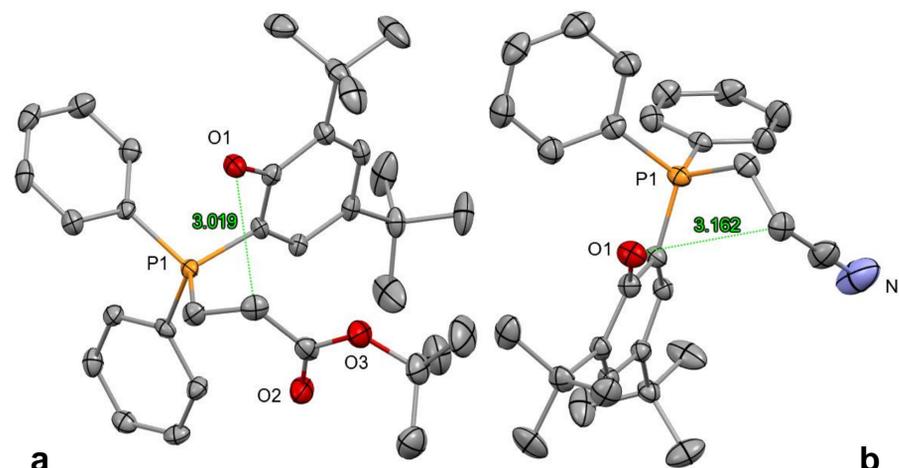
Overlay of the ¹H-NMR spectra of ortho-hydroxy phosphine (red) and the zwitterion formed with acrylonitrile (blue), characteristic proton signals marked by colored circles in the corresponding compound

The zwitterion formation can be observed with NMR-spectroscopy as a series of new signals appear, when compared to the parent phosphine. These signals are quite characteristic such as the curious multiplets observed at 3.1 and 3.3 ppm (red circle) that feature H-H as well as P-H couplings. The aromatic proton with its dd pattern at about 6.1 ppm (black circle) is also very characteristic as it is significantly upfield shifted when compared with the parent phosphine. With the appearance of these new peaks as well as the decline in the signal of the phenolic O-H (green circle), the conversion can be tracked over time.

Conclusion

In our research, a new class of compounds is investigated, namely ortho-hydroxy stabilized phosphine zwitterions. These compounds can be readily prepared from ortho-hydroxy phosphines and Michael-acceptors and offer the unique possibility to investigate the first intermediate of phosphine mediated nucleophilic Michael catalysis. Kinetic investigations are performed by UV-Vis spectroscopy, since all zwitterions have a strong absorption band at about 360 nm. First results include the characterization (NMR, X-ray crystallography) of these air and moisture stable compounds as well as first kinetic measurements, which indicate an acceleration of the reaction in protic solvents. This phenomenon presumably occurs because the proton transfer step is facilitated in protic media.

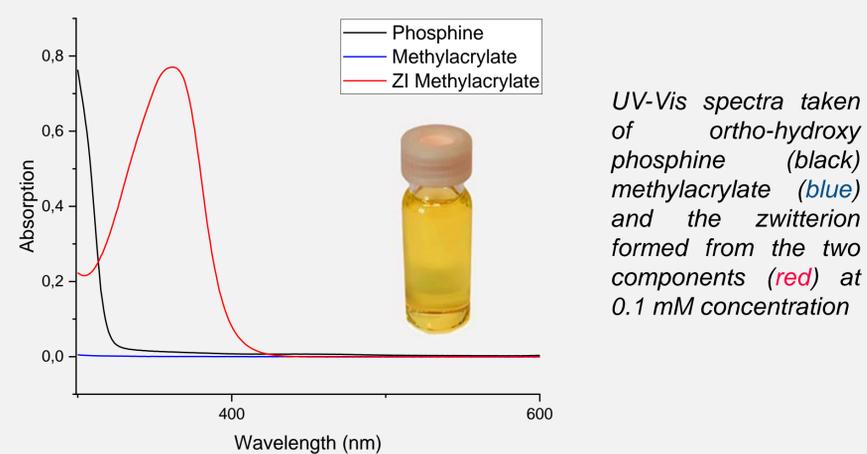
Crystal Structures



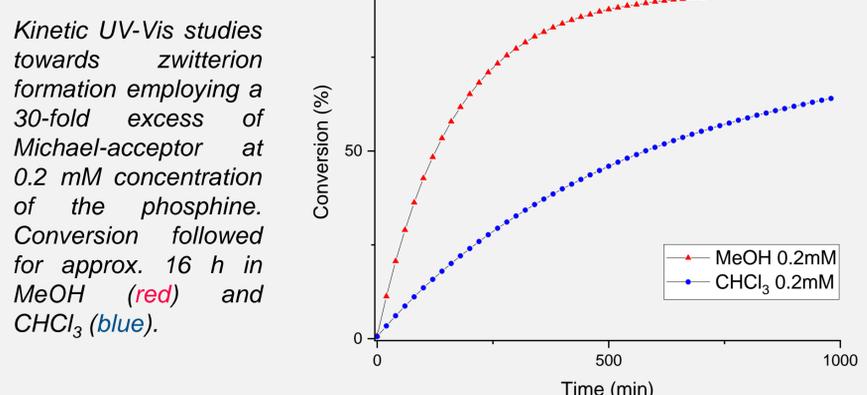
The molecular structures of zwitterions formed from ortho-hydroxy phosphine with tert-butyl acrylate (a) and acrylonitrile (b) featuring a possible interaction between the anionic oxygen and protons located on the CH₂ group (measured distances in green are well within the range for hydrogen bonds)³

Kinetic Studies

To investigate the parameters influencing the zwitterion formation, a broad kinetic study involving various Michael-acceptors and reaction conditions is necessary. Kinetic studies are performed via UV-Vis spectroscopy since the formed zwitterions show a characteristic absorption band around 360 nm.



UV-Vis spectra taken of ortho-hydroxy phosphine (black) methylacrylate (blue) and the zwitterion formed from the two components (red) at 0.1 mM concentration



First studies on the kinetics of the system focused on following the reaction of ortho-hydroxy phosphine with methyl acrylate in different solvents. It is evident that a protic solvent (like methanol) enhances the reaction rate and leads to higher conversion. This is likely due to the fact that the proton transfer from the phenolic group to the Michael- acceptor proceeds more rapidly in protic media.

References:

¹ Fischer, S. M.; Renner, S.; Boese, A. D.; Slugovc, C. *Beilstein J. Org. Chem.* **2021**, *17*, 1689–1697.

² Allgäuer, D. S.; Jangra, H.; Asahara, H.; Li, Z.; Chen, Q.; Zipse, H.; Ofial, A. R.; Mayr, H. *J. Am. Chem. Soc.* **2017**, *139*, 13318–13329.

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