# TCU Chemistry

Organic


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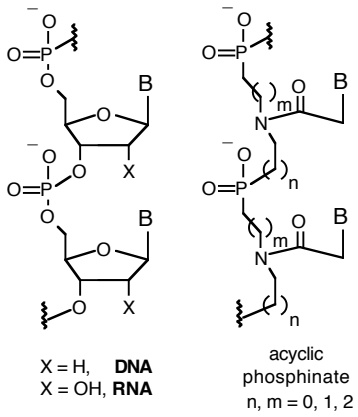
Medicinal

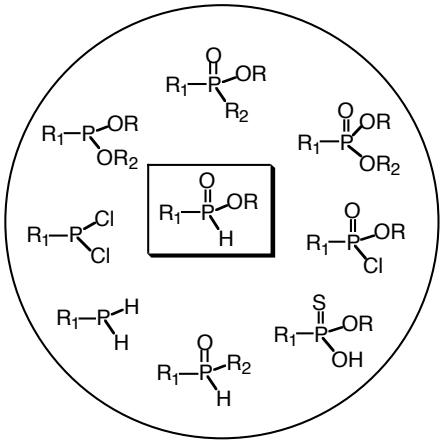
Our group's research interests are in the areas of organophosphorus chemistry, and bio-organic/medicinal chemistry. The core of our program in chemical biology focuses on the mechanism-based design, synthesis and evaluation of biologically active molecules such as enzyme inhibitors, receptors agonists and antagonists, and the development of novel antisense oligonucleotides with emphasis on the application of automated synthesis and combinatorial techniques




whenever possible.

*Medicinal Chemistry.* Unnatural compounds are synthesized to probe or modulate various biological processes. Applications of this research range from the elucidation of enzyme mechanisms to the preparation of molecules with potential medicinal use (anticancer, antiparasite, immunosuppressant, antisense, GABA analogs, bisphosphonates). One such medicinally oriented goal is the preparation and evaluation of new hydrolytically stable antisense oligonucleotides for sequence specific complexation to RNA and DNA targets. Also, current investigations aiming at the modulation of GABA receptors with phosphinic analogs are relevant to the treatment of various central nervous system (CNS) disorders. Another area is the study of H-phosphinates as precursors of biologically active phosphonates and bis-phosphonates. Finally, a collaborative project with TCU's Professor Coffer has also been initiated to prepare the recognition component of biocompatible calcified nanoporous silicon sensor arrays.

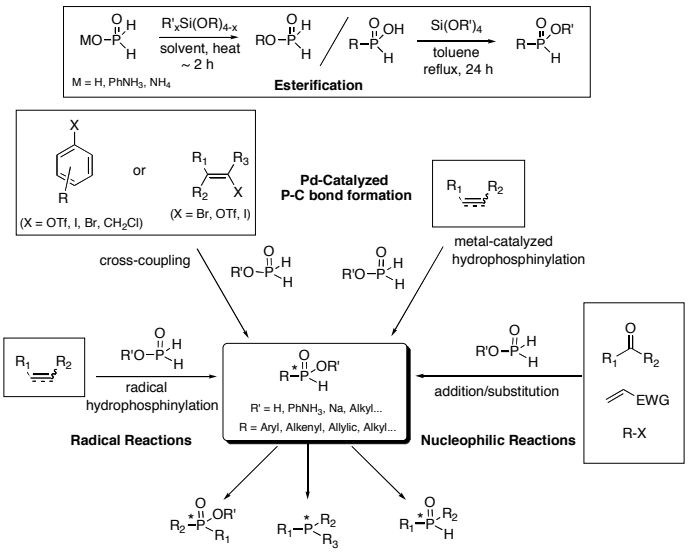
*Organophosphorus Chemistry.* Our second research interest concerns general organophosphorus chemistry and synthetic methodology which is driven by two main objectives: firstly, the synthesis of P-chiral compounds to be ultimately used in catalytic asymmetric transformations, including transition metal-catalyzed reactions, and secondly, the building of a methodology based on phosphorus compounds for organic synthesis as well as for the preparation of compounds possessing potential biological activity.



Our program toward the development of new methodology for the synthesis of H-phosphinic acids has led to several novel reactions, including the palladium-catalyzed cross-coupling of hypophosphorous derivatives with aryl, benzylic, and alkenyl electrophiles, and the room temperature radical addition of hypophosphites to olefins. More recently we have uncovered new catalytic phosphorus-carbon bond-forming reactions via the hydrophosphinylation of unsaturated compounds, using palladium and nickel catalysts. All our reactions are applied to the synthesis of biologically active compounds. Asymmetric versions of these new reactions are also being developed for the preparation of P-chiral building blocks.

Combining the above research directions in the same research program provides valuable advantages. Because phosphorus is ubiquitous in nature, a variety of molecules can be designed to achieve some specific biological effect. To achieve the efficient synthesis of such compounds, new

synthetic routes will be required, which could borrow from independently-developed methods. Because of our interests in the preparation of phosphorus-containing biologically-actice compounds, target-driven methodology development is also conducted in our laboratory. In general, a combination of organic synthesis, methodology, and chemical biology, will be used to pursue our objectives.




*Selected Publications*


"Direct Monoalkylation of Alkyl Phosphinates to Access H-Phosphinic Acid Esters", Abrunhosa-Thomas, I.; Ribière, P.; Adcock, A. C.; Montchamp, J.-L. *Synthesis* In press.

"Radical Reaction of Sodium Hypophosphite with Terminal Alkynes: Synthesis of 1,1-bis-H-Phosphinates", Gouault-Bironneau, S.; Deprèle, S.; Sutor, A.; Montchamp, J.-L. *Org. Lett*. **2005**, *7*, 5909.

"$NiCl_2$-Catalyzed Hydrophosphinylation", Ribière, P.; Bravo-Altamirano, K.; Antczak, M.; Hawkins, J. D.; Montchamp, J.-L. *J. Org. Chem*. **2005**, *70*, 4064.

"Palladium-Catalyzed Phosphorus-Carbon Bond Formation: Cross-Coupling Reactions of Alkyl Phosphinates with Aryl, Heteroaryl, Alkenyl, Benzylic, and Allylic Halides and Triflates", Bravo-Altamirano, K.; Huang, Z.; Montchamp, J.-L. *Tetrahedron* **2005**, *61*, 6315.

"Recent Advances in Phosphorus-Carbon Bond Formation: Synthesis of H-Phosphinic Acid Derivatives from Hypophosphorous Compounds", Montchamp, J.-L. *J. Organomet. Chem*. **2005**, *690*, 2388.

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"Triethylborane-Initiated Room Temperature Radical Addition of Hypophosphites to Olefins: Synthesis of Monosubstituted Phosphinic Acids and Esters" Deprele, S.; Montchamp, J.-L *J. Org. Chem*. **2001**, *66*, 6745.



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