

Highly Enantioselective Synthesis of 3,4-Dihydropyrans through a Phosphine-Catalyzed [4+2] Annulation of Allenones and β,γ -Unsaturated α -Keto Esters

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Phosphine-catalyzed cyclization reactions are of enormous synthetic value, evidenced by the ubiquitous presence of ring structures in natural products and bioactive molecules. Over the last few years, the group of Professor Yixin Lu at the National University of Singapore has been interested in developing novel and versatile organic catalysts that can be readily derived from amino acids. Thus, explained Professor Lu, one of the main research efforts of his group is to devise powerful approaches to access chiral ring motifs, especially those structures that are not yet accessible via existing methods, and the dihydropyrans synthesized in this paper are important skeletons of biological significance. Professor Lu said: “In the area of phosphine catalysis, we designed a series of amino acid based bifunctional phosphines and demonstrated their effectiveness for a wide range of reactions, including (aza)-MBH

reactions, various [3+2] cycloadditions, [4+2] cyclization, [4+1] annulation, asymmetric allylic alkylation, phosphine-mediated Michael addition, and γ -addition. Our catalysts can be easily assembled and the structures are highly tunable, and such features are crucial in asymmetric catalysis as a ‘universal’ catalyst does not exist.”

Professor Lu explained: “In phosphine catalysis, it is imperative to expand the scope of substrates suitable for phosphine activation. While allene esters have been widely employed, utilization of allene ketones is rare. This paper documents an unprecedented utilization of allenones as a reaction partner. The reaction system is complex,” continued Professor Lu, “and achieving the desired [4+2] cyclization was quite tricky.” Professor Lu explained that the activation of allenones by phosphines creates a phosphonium enolate,

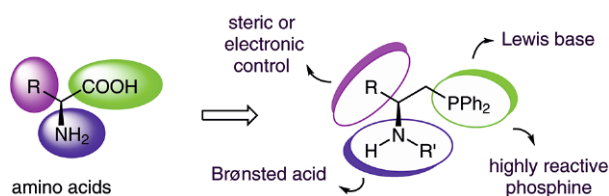


Figure 1

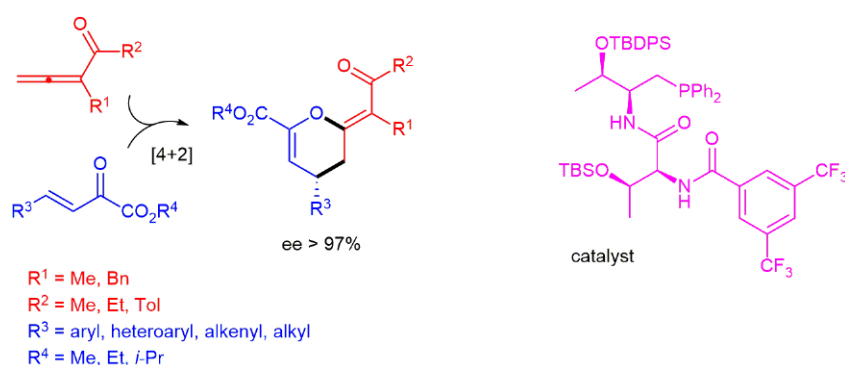


Figure 2

which possesses different resonance forms. “The subsequent advanced intermediate generated upon addition of the enolate anion to an electrophile also has different reaction pathways. In this paper, we suppressed undesired modes of reaction by careful selection of reaction systems,” he added.

This work not only demonstrates an unprecedented utilization of allenones as a reaction partner, but also represents the first asymmetric synthesis of dihydropyrans via phosphine catalysis. “We hope this work will lead to the discovery of more novel approaches to access oxygen-containing ring structures via phosphine catalysis,” said Professor Lu.

“The complexity in phosphine-catalyzed reaction systems is challenging, but also truly exciting. Discoveries on new reactions and novel modes of activations are well anticipated, if one can discern subtle mechanistic differences and design catalytic systems accordingly,” he concluded. ■

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About the authors



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Weijun Yao was born in Zhejiang (P. R. of China) in 1983. He received his B.Sc. and Ph.D. (under the supervision of Professor Cheng Ma) from Zhejiang University in 2006 and 2011, respectively. Currently, he is a postdoctoral fellow working with Professor Yixin Lu at National University of Singapore (NUS).



Dr. X. Dou

Xiaowei Dou was born in Shandong (P. R. of China) in 1987. He received his B.Sc. from Nanjing University (P. R. of China) in 2009, and he then joined the research group of Professor Lu at NUS. He received his Ph.D. in 2013, and he is now working with Professor Tamio Hayashi as a postdoctoral fellow at NUS.



Prof. Y. Lu

Yixin Lu received his Ph.D. from McGill University (Montreal, Canada) under the supervision of the late Professor George Just in 2000. He then carried out post-doctoral research with Professor Peter W. Schiller at the Clinical Research Institute of Montreal (Canada), and subsequently worked as an RCMS fellow with Professor Ryoji Noyori at Nagoya University (Japan). He joined the Department of Chemistry, NUS, in September 2003 where he is now a professor.