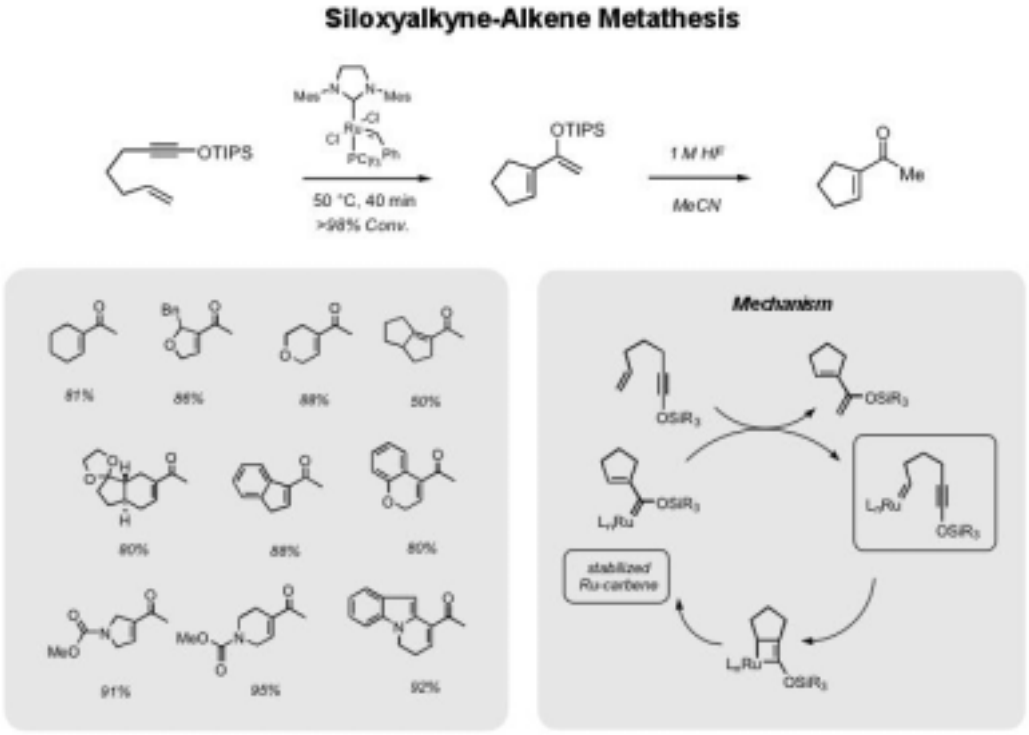
A Three-Dimensional Array for Multiparallel Synthesis

Sergey A. Kozmin
Department of Chemistry, University of Chicago
http://chemistry.uchicago.edu/fac/kozmin.shtml

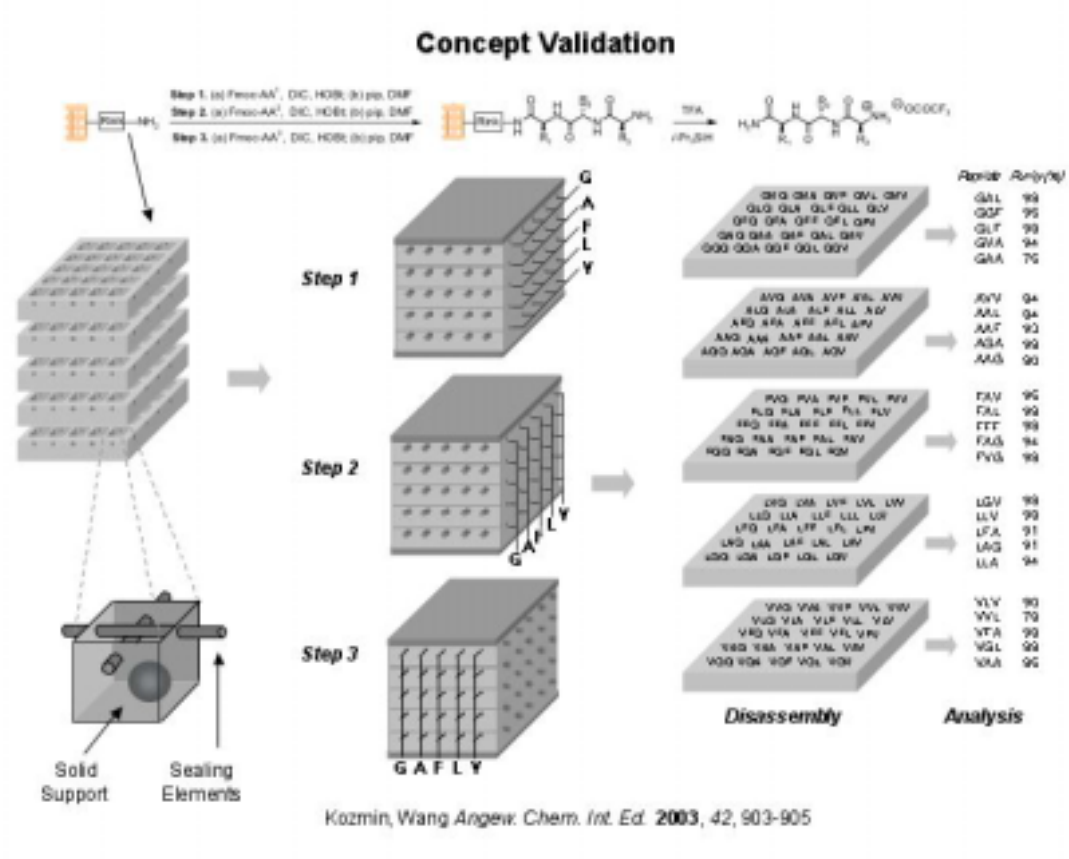
Diversity-oriented synthesis combined with high-content screening has emerged as a valuable strategy for the discovery and optimization of new agents capable of modulating complex metabolic and signaling pathways. "High-diversity" small-molecule libraries, which are based on multiple skeletal frameworks, are valuable for broad high-throughput biological screening. Development of parallel synthetic strategies that would enable efficient variation of the scaffold architecture represents a significant challenge. Solution of this complex problem would enable rapid production of highly diverse chemical libraries that would facilitate identification of new biologically active compounds.



Schramm, Reddy, Kozmin *Angew. Chem. Int. Ed.* **2001**, *40*, 4274

We will describe the synthesis of 1160-member library that incorporates 20 structurally diverse scaffolds. The development of this strategy was enabled by our recently disclosed siloxyalkyne-alkene metathesis. Our approach was designed to provide rapid entry into a variety of polycyclic frameworks via significant structural variations of the building blocks employed during the initial series of cycloadditions.

In addition, we will describe a novel concept for multiparallel synthesis, which entails a three-dimensional delivery of reactants to an array of interconnected reaction wells. Conceptually similar to the split-and-pool synthesis, this method, however, eliminates the additional encoding-decoding manipulations and offers improved throughput compared to the conventional robotically driven parallel synthesis.



Recent references

Reddy, D. S.; Kozmin, S. A. Efficient and General Approach to Eremophilanes Using Siloxyalkyne-Alkene Metathesis. *J. Org. Chem.* **2004**, *69*, *ASAP*

Sweis, R.; Schramm, M. P.; Kozmin, S. A. Silver-Catalyzed [2+2] Annulations of Siloxyalkynes with Simple Enones and Enoates. *J. Am. Chem. Soc.* **2004**, *126*, 7442-7443