Development and synthetic application of the allylbis (silane) cyclization terminator
by Timothy Scott Kercher

A thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry
Montana State University
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Abstract:
In order to advance the existing methodology of allylsilane-terminated cyclizations, a series of amino-allyl(bis)silanes was prepared for use as intermediates in route to cationic cyclizations terminated by the novel allyl(bis)silane nucleophile. This terminator was found to readily participate in the intramolecular trapping of activated imines and C-acylnitrilium ions providing highly substituted and functionally diverse pyrrolidines, piperidines and pyrrolines. These processes occurred not only in high chemical efficiency under mild conditions but with excellent levels of regioselectivity and substrate based stereocontrol.

As a result, this methodology was successfully applied to the stereoselective synthesis of biologically active isotropane alkaloids and the azapolycyclic core of the potent natural insecticide, stemofoline. These applications demonstrated the ability of the allyl(bis)silane terminator to engage in tandem silicon-directed cyclizations. Such reactivity was not possible with the silane terminators previously used by synthetic chemists.

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APPROVAL

of a thesis submitted by

Timothy Scott Kercher

This thesis has been read by each member of the thesis committee and has been found to be satisfactory regarding content, English usage, format, citations, bibliographic style and consistency, and is ready for submission to the College of Graduate Studies.

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Date April 22, 1997

To all of my wonderful family

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ABSTRACT

In order to advance the existing methodology of allylsilane-terminated cyclizations, a series of amino-allyl(bis)silanes was prepared for use as intermediates in route to cationic cyclizations terminated by the novel allyl(bis)silane nucleophile. This terminator was found to readily participate in the intramolecular trapping of activated imines and C-acylnitrilium ions providing highly substituted and functionally diverse pyrrolidines, piperidines and pyrrolines. These processes occurred not only in high chemical efficiency under mild conditions but with excellent levels of regioselectivity and substrate based stereocontrol.

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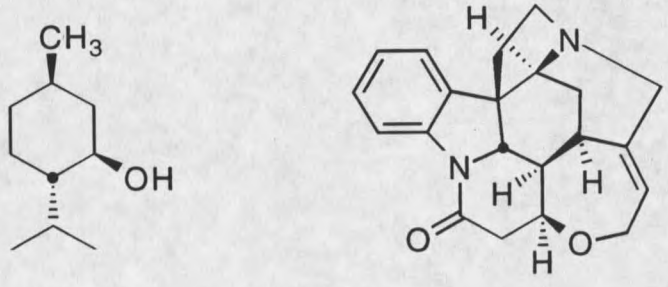
INTRODUCTION

A vast proportion of the molecular targets of interest to the synthetic organic chemist such as natural products, pharmaceuticals and synthetic intermediates contain cyclic or polycyclic carbon frameworks. The degree of complexity of these cyclic arrays of atoms may range drastically. This becomes evident upon comparing menthol, a simple monocyclic terpene used as peppermint flavoring, to the formidable heptacyclic structure of the powerful poison, strychnine (Figure 1). It is therefore no surprise that carbon-carbon bond formation in an intramolecular fashion has been the crux of countless past and present research endeavors in the field of organic chemistry.

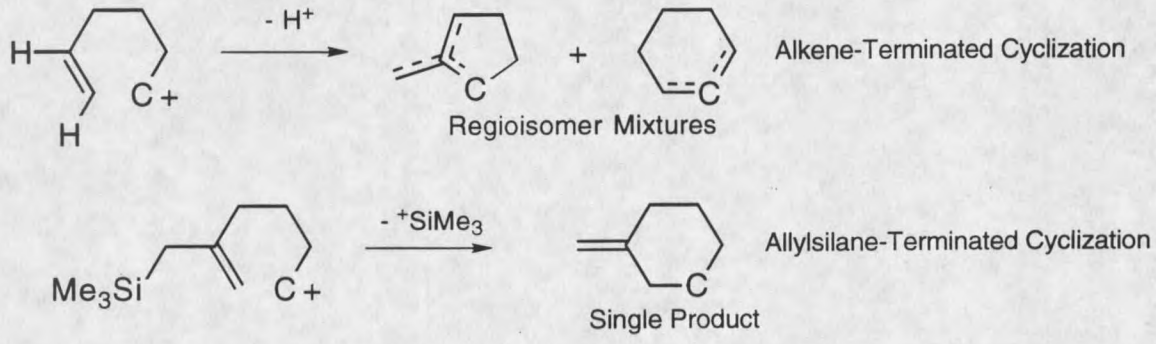


Menthol Strychnine

Figure 1. Well Known Cyclic Molecules

The classical method for formation of such important bonds has involved the intramolecular trapping of a reactive carbon electrophile, termed the initiator, by a suitably disposed nucleophilic carbon or terminator. From a standpoint of the terminator, alkenes and alkynes have been extensively applied by virtue of the nucleophilicity of their pi electron clouds. It has been demonstrated over the course of research involving alkene terminators that,

unless the cyclization substrate is carefully chosen, alkene-terminated cyclizations generally result in mixtures of products. This problem originates from lack of sufficient regiocontrol in both the ring formation and elimination steps of the cyclization reaction resulting in products of various ring size and position of unsaturation respectively. Competitive reactions such alkyl and hydrogen shifts have also been shown to commonly occur, further complicating the product mixture. Fortunately, it eventually became realized that by using an alkene appended to a silane moiety, as in an allylsilane, these types of cationic cyclizations may be directed through a single reaction pathway giving rise to a single reaction product (Scheme 1).



Scheme 1

As a result of this observation that a strategically located silicon atom has a dramatic effect on the course of cationic cyclizations and electrophilic additions in general, a host of silicon terminators has evolved over the years (Figure 2). These nucleophiles are in constant use today in both the intramolecular and intermolecular formation of strategic bonds employing a broad spectrum of electrophiles. More specifically, the cationic cyclization

reaction has become a more versatile and efficient synthetic tool finding broad application in the synthesis of many types of cyclic molecules.

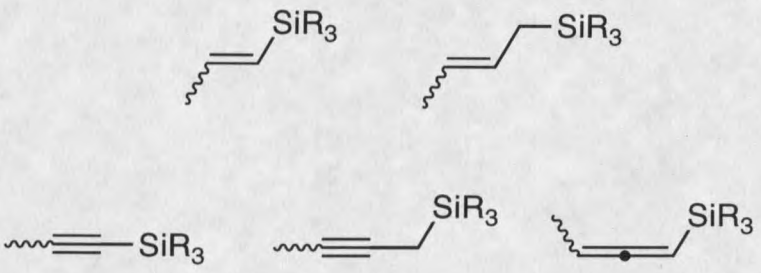


Figure 2. Silicon-Based Terminators

Despite the tremendous amount of development, there is still a strong motivation for continuing the evolution of silicon-directed cyclizations. The standards of modern synthetic chemistry demand not only regioselectivity but diastereo- and enantioselectivity from a reaction as well. Polyfunctionalization and sensitive groups in substrates also renders the need for terminators that engage under mild conditions. Ultimately, practical and concise syntheses of molecular targets of high topological complexity might be realized using silicon based terminators with the ability to direct not just a single cyclization but multi-cyclizations as well. Thus it became the goal of this research to develop a silane terminator that could potentially satisfy these criteria of today's synthetic methods. It was conceived that an allylbis(silane) terminator might meet this challenge and eventually be applicable to the synthesis of polycyclic alkaloids, particularly in the construction of the azatricyclic core of the alkaloid stemofoline (Figure 3).