Tetrahedron Letters,Vol.27,No.27,pp 3115-3118,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

CHELATION-CONTROLLED CYCLIZATION OF β-KETOESTER-SUBSTITUTED AND β-KETOAMIDE-SUBSTITUTED ALLYLSILANES.

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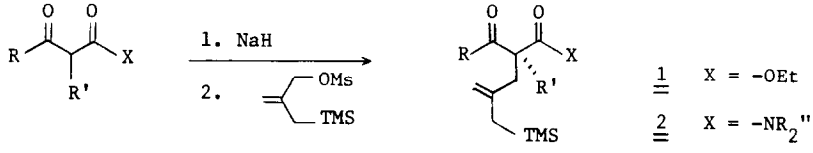
Abstract: The first examples of Lewis acid-catalyzed chelation-controlled cyclization reactions are reported. Titanium tetrachloride-initiated cyclization of β-ketoester and β-ketoamide-substituted allylsilanes proceeds in isolated yields of 65-88%, providing a single diastereomeric product in each case.

With few exceptions, conventional approaches to carbocyclic ring systems involve two separate and distinct phases. Construction of a minimally elaborated ring is first carried out to establish the carbon skeleton. Subsequent manipulation of functionality and stereochemistry on this carbocycle follows, taking advantage of inherent conformational and steric factors in order to incorporate necessary substitution patterns. In contrast, we have initiated a program aimed toward development of synthetic methods allowing ring formation with concomitant stereochemical control of substituents. Herein we describe our initial efforts in this area, utilizing intramolecular chelation-controlled addition of allylsilanes to carbonyl substrates.

Chelation-control of stereochemistry is perhaps the most effective means by which diastereoselective carbonyl addition reactions can be accomplished.[1] A further advantage of this technique is that the sense of relative asymmetric induction is easily predicted based on a simple model. Chelation-control is ideal for processes in which complexing metals are intimately involved in the carbon-carbon bond-forming process. Lewis acid-catalyzed <u>intermolecular</u> addition of allylsilanes[2] and allylstannanes[3] with carbonyl substrates are prime examples demonstrating the efficiency of this process. However, while diastereoselective cyclizations utilizing allylsilanes have been reported previously,[4] to the best of our knowledge there has been no attempt to apply <u>intramolecular</u> chelation control to the stereocontrolled generation of carbocyclic ring compounds.

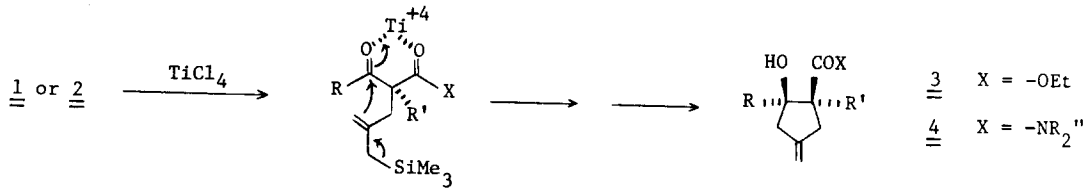
We chose β-ketoester- and β-ketoamide substrates to illustrate the feasibility of this approach to stereodefined carbocycles. Allylsilanes suitably functionalized for cyclization were prepared by straightforward alkylation reactions.[5]



1 X = -OEt

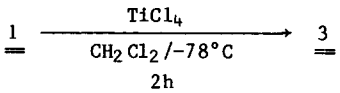
2 X = $-NR_2''$

β-Dicarbonyl substrates were expected to be effective chelators of Ti^{+4}, and thus we anticipated high diastereoselectivity in the cyclization process.



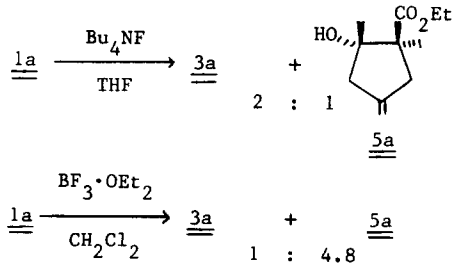
Cyclizations effected by treatment of substrates with $TiCl_4$ in CH_2Cl_2 have been extremely successful. A wide range of β-ketoester substrates successfully undergo cyclization (Table I).[6]

Table I. Lewis Acid-Catalyzed Cyclization of β-Ketoester-Substituted Allylsilanes.

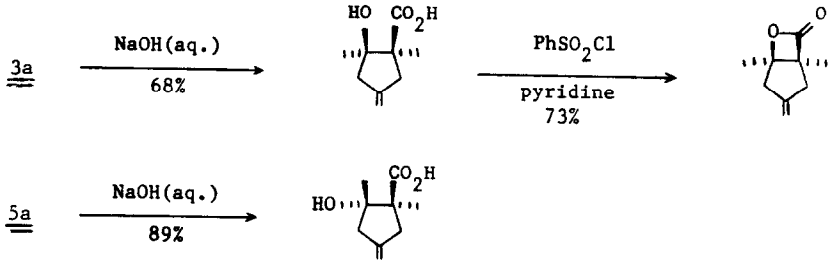


Starting Material	R	R'	% Isolated Yield
1a	Me	Me	88
1b	Et	Me	78
1c	iPr	Me	66
1d	tBu	Me	74
1e	Ph	Me	73
1f	Me	Et	78
1g	Me	Ph	73
1h	Me	iPr	65

Careful gas chromatographic studies have been conducted on all crude reaction mixtures. We are unable to detect diastereomeric products in any of these reactions. Preliminary evidence suggests that these reactions are under kinetic control, with no equilibration of diastereomers due to a retroaldol-aldol process.[7] Thus, reaction of **1a** with $TiCl_4$ was followed with time from less than one minute to a period of hours, and no diastereomer could be detected at any time during this period. Fluoride-induced cyclization of **1a** led to generation of a 2:1 mixture of diastereomers,[5b,8] while $BF_3 \cdot Et_2O$ (a non-chelating Lewis acid) provided a 1:4.8 mixture of diastereomers.[2c,3c]

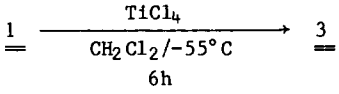


Stereochemistry of products in this series was established by hydrolysis of 3a to the corresponding carboxylic acid, followed by generation of the β-lactone.[9] Diastereomer 5a could be hydrolyzed to the corresponding hydroxyacid, which is incapable of forming a β-lactone. All other compounds were correlated to 3a by spectroscopic techniques.



β-Ketoamides are also effective substrates for the reaction (Table II). As in the

Table II. Lewis Acid-Catalyzed Cyclization of β-Ketoamide-Substituted Allylsilanes.



Starting Material	R	R'	R"	% Isolated Yield
2a	Me	H	Et	65
2b	Et	H	Me	57
2c	iPr	H	Me	56
2d	tBu	H	Me	75
2e	Me	Me	Et	100

β-ketoester series, single diastereomers were detected by gas chromatographic analysis of crude reaction mixtures, and these appear to reflect kinetic product ratios. Spectroscopic techniques were utilized to correlate stereochemistry of 4 to (1R*,2S*)-N,N-dimethyl-2-tert-butyl-2-hydroxycyclopentanecarboxamide, the single crystal X-ray structure of which has been determined.[10]

To the best of our knowledge, this represents the first time that chelation-control has been utilized to influence stereochemistry in cyclization reactions. The predictably high diastereoselectivity of chelation-controlled reactions, coupled with the variety of ring sizes and substitution patterns that can be accessed by such processes, promise to make further use of this technique of great importance for construction of complex carbocyclic ring systems.

Acknowledgement. We wish to thank the National Institutes of Health (GM 35249) for support of this research. An instrumentation grant from the National Institutes of Health (RR 01709) is also gratefully acknowledged.

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6. β-Ketoesters 1 with R' = H also undergo reaction in approximately 60% yields, accompanied by uncyclized protodesilylation product. Experiments with β-formylesters and other substrates are in progress and will be reported in a full paper.

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(Received in USA 19 March 1986)