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Tandem Aldol−Allylation and Aldol−Aldol Reactions with Ketone-Derived Enolsilanes: Highly Diastereoselective Single-Step Synthesis of Complex Tertiary Carbinols

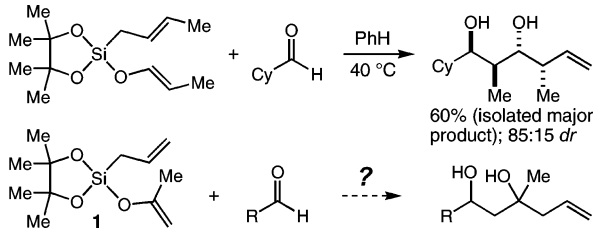
Xiaolun Wang, Qinglin Meng, Nicholas R. Perl, Yue Xu, and James L. Leighton*

Department of Chemistry, Columbia University, New York, New York 10027

Received June 1, 2005; E-mail: leighton@chem.columbia.edu

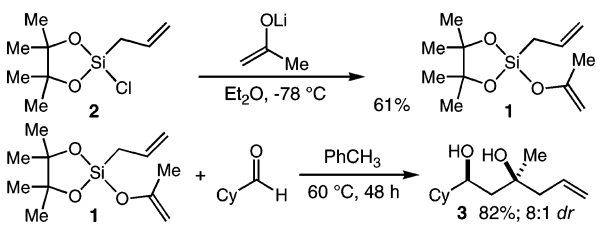
As part of a program dedicated to the development of tandem reactions for the rapid synthesis of polyketide natural products, we have reported a new tandem aldol−allylation reaction that can deliver polyketide fragments with up to four stereocenters in a remarkably simple reaction that owes its success to the Lewis acidity induced in the silane by the strained pinacolate ring (Scheme 1).[1] In analyzing ways to expand the scope of this reaction, we noted the occurrence of tertiary carbinols in important polyketide natural products (e.g., the spongistatins[2]), which suggested the use of ketone-derived enolates as the enol component of the tandem reagents (e.g., **1**, Scheme 1). Type I[3] allyl- and crotylsilane additions to ketones are known[4] but have not previously been described as part of a tandem reaction of the type proposed here. Herein we report the realization of this idea, as well as a new, related reaction involving ketone-derived enolates, the tandem aldol−aldol reaction. In all cases, stereochemically and structurally complex polyketide-like tertiary carbinols may be obtained from aldehydes in an operationally trivial and highly diastereoselective tandem reaction.

Scheme 1



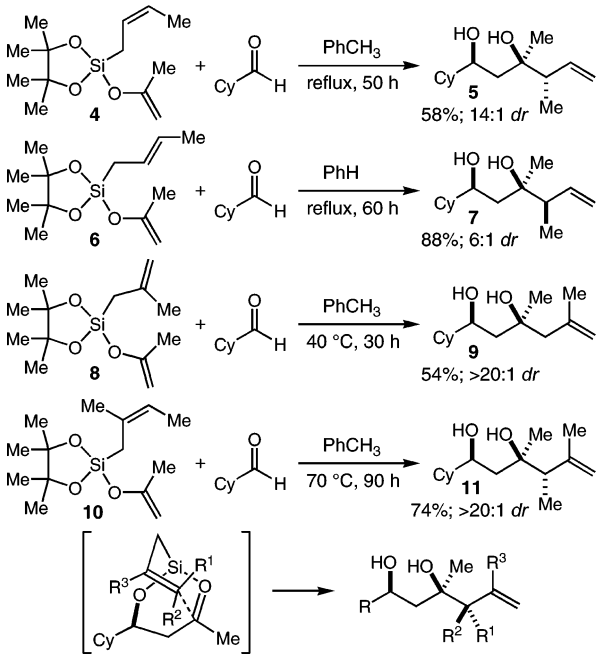
Our studies began with the synthesis of allylenolsilane **1** (Scheme 2). Chlorosilane **2** was treated with the lithium enolate derived from acetone to give **1** in 61% yield. Treatment of CyCHO with 1.5 equiv of **1** in toluene at 60 °C for 48 h gave diol **3** in 82% yield and with 8:1 diastereoselectivity favoring the *syn*-diol diastereomer. As expected, and unlike some of the previously described aldehyde-derived allylenolsilanes,[1] <2% of the product resulting from direct allylation of the aldehyde was observed.

Scheme 2



A survey of the scope with respect to substitution on the allyl fragment was undertaken (Scheme 3). Both *cis*- and *trans*-crotyl fragments participated smoothly in the tandem reaction, allowing the synthesis of stereochemically complex diols (**4** → **5** and **6** → **7**). A methallyl fragment was also found to be a viable participant in the tandem reaction (**8** → **9**), leading to a significantly faster and highly diastereoselective reaction, although in this case, a significant amount (19%) of the simple aldehyde methallylation product was also observed. Finally, the methallyl and *cis*-crotyl substitutions may be combined as in silane **10**, leading to the highly diastereoselective synthesis of diol **11** in 74% yield. The illustrated chairlike transition state (pinacol omitted for clarity) for the allyl-/crotylation step correctly rationalizes the simple diastereoselectivity of crotylation products **5**, **7**, and **11** and is similar to a model advanced by Chemler and Roush in their detailed examination of intramolecular crotylsilylations.[5] However, the observed preference for the allyl-/crotylation to occur *cis* to the cyclohexyl group leading to *syn*-1,3-diols is not well-understood and, indeed, stands in contrast to the corresponding intramolecular allylborations.[6]

Scheme 3



Extensive investigations have revealed that tandem aldol−allylation reagents constructed from 1,2-*N*-alkylamino alcohols or 1,2-*N*,*N*′-dialkyldiamines, as opposed to 1,2-diols as above, provide little or no diol (tandem) products in reactions with aldehydes. Reasoning that the basic amine group is the source of the problem, we have investigated less basic *N*-aryl amino alcohols. After considerable experimentation, allylenolsilane **12** was prepared (as a 3:1 mixture of diastereomers), and we were delighted to find not only that it participated in a smooth tandem aldol−allylation

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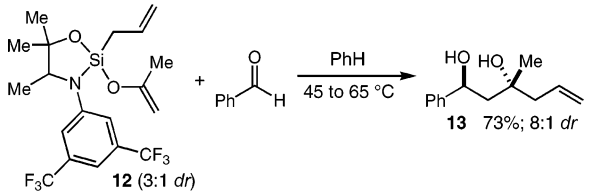
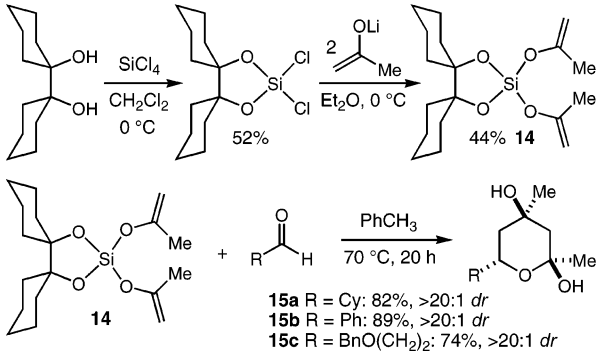
Scheme 4



reaction with benzaldehyde but also that the 1,3-*anti* diol **13** was the major product with 8:1 diastereoselectivity (Scheme 4). Although the fact that **12** is prepared as a 3:1 mixture of diastereomers is a complicating feature of this silane design, this experiment nevertheless demonstrates that the design of tandem aldol−allylation reagents that give stereochemical flexibility is possible.

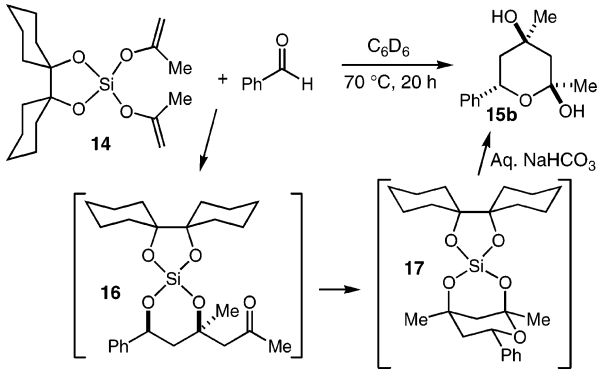
These successes with ketone-derived enolates within the strained silacycle paradigm raised the possibility of a tandem aldol−aldol reaction using a dienolsilane. While several groups have successfully and elegantly orchestrated one-pot sequential aldol reactions,[7] and one group has reported tandem aldol−aldol reactions using various metal dienolates,[8] the scope of these reactions is quite narrow and the development of a more general system remains an elusive and enticing goal. Thus, to investigate the ability of our silane system to participate in a smooth tandem aldol−aldol reaction, we prepared dienolsilane **14** as outlined in Scheme 5. The use of bicyclohexyl-1,1′-diol instead of pinacol was due to the success of the former (and failure of the latter) in the reaction with $SiCl_4$. With **14** in hand, the reactions with three aldehydes were investigated. As shown, the reactions proceeded smoothly, delivering hemiketals **15a**−**c** in high yields and with excellent diastereoselectivity. These efficient and selective reactions have potential relevance to the synthesis of tetrahydropyrans, such as are found in polyketide natural products.

Scheme 5



When the reaction of silane **14** with benzaldehyde was carried out in benzene-d_6 as solvent, the reaction could be monitored by ^{1}H NMR spectroscopy, and a set of signals grew in, consistent with the expected structure **16** (Scheme 6). Over time, however, the signals for **16** gave way to a new set of signals we have assigned to structure **17**.[9] In principle, this rearrangement provides a built-in sequestering mechanism for the carbonyl product of the tandem aldol−aldol reaction (e.g., the ketone in **16**), preventing it from reacting with reagent **14**. While ketone **16** would not be expected

Scheme 6



to be competitive with an aldehyde for the attentions of reagent **14**, it may reasonably be posited that such a sequestering mechanism could become important in the design of a tandem aldol−aldol reaction with *aldehyde*-derived dienolsilane reagents.

New tandem aldol−allylation reactions have been described, employing enolsilanes derived from ketones, leading to the diastereoselective synthesis of complex tertiary carbinols. In addition, a new and highly efficient and diastereoselective tandem aldol−aldol reaction has been described. These operationally simple reactions provide remarkably efficient access to complex structures with relevance to biologically important polyketide natural products. Current efforts are focused on the development of enantioselective and/or diastereoselective (using chiral aldehydes) variants of these powerful reactions.

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Supporting Information Available: Experimental procedures, characterization data, and stereochemical proofs. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Rearrangement of the initially formed diol/diolate to the corresponding hemiacetal/ketal appears to be a common feature in sequential/tandem aldol−aldol reactions. See refs 7 and 8.

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