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# Synthetic Stitching with Silicon: Geminal Alkylation−Hydroxylation of Alkynyl Carbonyl Compounds

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Silicon tethers have been used extensively in organic synthesis as a means of achieving reactivity, chemoselectivity, and stereoselectivity through proper orientation of reagents in an intramolecular fashion.[1] An alternative method to employing a silicon tether is to internally deliver an alkyl group, which, if combined with a C−Si to C−O transformation, can regio- and diastereoselectively "stitch" together geminal C−C and C−O bonds at the $\beta$-position with respect to an electron-withdrawing group. In this report, we demonstrate the feasibility of this strategy for a new synthesis of $\beta$-carbonyl-substituted tertiary alcohols from $\alpha,\beta$-alkynyl ketones and esters. The unique features of these products make them challenging synthetic targets. The addition of organometallic species to carbonyl compounds is a typical route to tertiary alcohols, but is generally unsuccessful for enolizable 1,3-dicarbonyl compounds.[2] Aldol additions to ketone electrophiles also encounter difficulties not present with aldehyde acceptors.[3] Alternative methods of synthesizing this structural class would therefore be useful.[4]

As outlined in Scheme 1, (*Z*)-$\beta$-silyl-enones and enoates (**4**) with appropriate substituents on silicon, upon treatment with a fluoride anion and water, may undergo a 1,2-Si → C migration of a carbon substituent on the silicon, resulting in the formation of a tertiary silane **3**. We were excited by the prospect that oxidation of the stable silanes (**3**) might allow facile access to tertiary alcohols **2**. The approach requires the realization of three steps: (1) selective hydrosilylation of alkynyl esters and ketones, (2) selective 1,2-Si → C migration, and (3) chemoselective oxidation of a highly hindered tertiary silane.

An important condition for the synthetic utility of any method based on such a Si−C migration is the ready synthetic access to the requisite (*Z*)-$\beta$-silyl-enones and enoates (**4**). Indeed, ruthenium-catalyzed hydrosilylation of $\alpha,\beta$-alkynyl carbonyl compounds provides highly selective access to vinylsilanes **4**. Hydrosilylation of internal alkynes in general is a poorly understood process, and without directing heteroatoms, our own experience with obtaining regioselectivity with internal alkynes is mixed.[5] However, the use of catalytic $[Cp^*Ru(MeCN)_3]PF_6$ in the hydrosilylation of alkynyl esters and ketones provides exclusive trans addition to form the (*Z*)-olefin isomer, with very good selectivity for the $\beta$-silyl regioisomer (Table 1). Similar regiochemistry is accessible by stoichiometric silyl-cupration of the alkyne, but the silyl group is generally limited to $SiMe_2Ph$, the basic silylcuprate prevents tolerance of some functional group, and direct hydrosilylation is a more atom economical process.[6]

A variety of substituted silanes can be employed. Although $\gamma$-alkoxy groups result in generally lower yields or turnover numbers (Table 1, entries 7 and 12), the unprotected $\gamma$-hydroxy compounds are well-tolerated (Table 1, entries 8−11). An alkynyl acid is also a good substrate for hydrosilylation (Table 1, entry 13). Interestingly, only 1.2 equiv of silane need to be employed with the carboxylic acid functionality, a fact that demonstrates the chemoselectivity of the ruthenium-catalyzed reaction.

***Scheme 1.*** Approaches to $\beta$-Carbonyl-Substituted Tertiary Alcohols

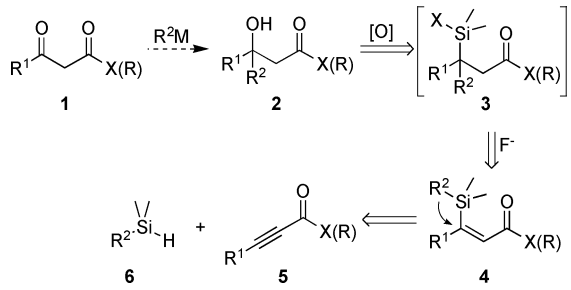
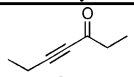
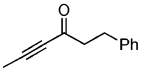
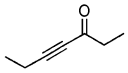
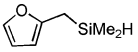
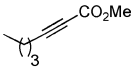
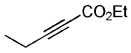
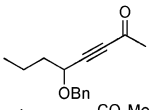
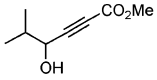
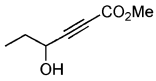
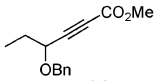
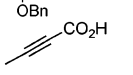



***Table 1.*** Hydrosilylation of Alkynyl Carbonyl Compounds[a]

| entry | alkyne | silane | Ru (mol%) | yield[a] | selectivity[b] |
|---|---|---|---|---|---|
| 1 |  | $BnMe_2SiH$ | 0.5 | 98 | >20:1 |
| 2 |  | $(allyl)Me_2SiH$ | 4 | 81 | >20:1 |
| 3 |  |  | 5 | 89 | >20:1 |
| 4 |  | $BnMe_2SiH$ | 1 | 99 | >20:1 |
| 5 | | $(allyl)Me_2SiH$ | 2 | 85 | >20:1 |
| 6 |  | $PhMe_2SiH$ | 2 | 96 | >20:1 |
| 7 |  | $BnMe_2SiH$ | 1 | 67 (89)[c] | >20:1 |
| 8 |  | $BnMe_2SiH$ | 1 | 86 | 7:1 |
| 9 | | $(allyl)Me_2SiH$ | 3 | 53 | 14:1 |
| 10 |  | $BnMe_2SiH$ | 2 | 88 | 11:1 |
| 11 | | $(allyl)Me_2SiH$ | 5 | 72 | 15:1 |
| 12 |  | $BnMe_2SiH$ | 3 | 34 | >20:1 |
| 13 |  | $BnMe_2SiH$ | 1 | 94 | >20:1 |

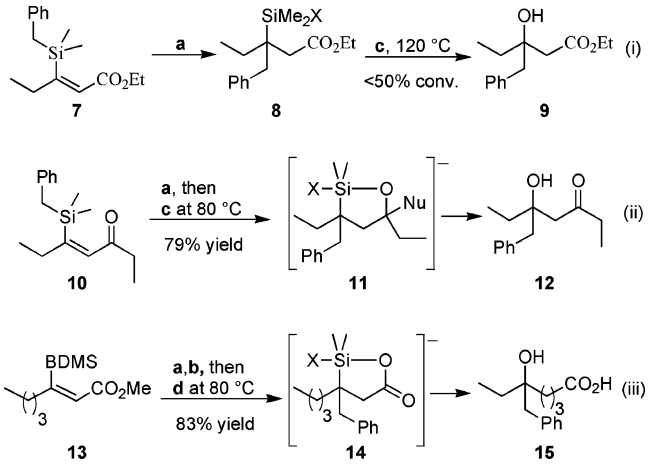
[a] Reactions performed using 1.2 equiv of silane at 0.5 M in acetone under $N_2$ for 30 min. Yields given for pure isolated $\beta$-silyl major product. [b] Ratio of $\beta$-vinylsilane:$\alpha$-vinylsilane determined by analysis of crude $^1H$ NMR. In all cases only (*Z*)-vinylsilane isomers were observed. [c] Yield in parentheses is based on recovered alkyne.

With a vinylsilane synthesis in hand, we turn to the oxidation of the tertiary silane intermediate (Scheme 2). It is well understood that steric hindrance has a significant effect on the success of alkyl



10.1021/ja045971j CCC: $27.50 

***Scheme 2.*** Establishing a Successful Geminal Stitching Protocol[a]



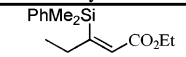
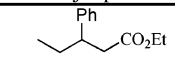
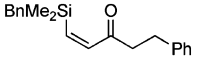
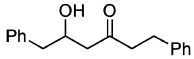
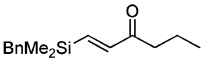
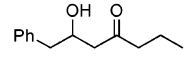
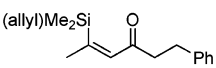
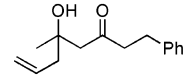
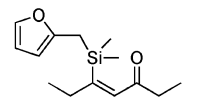
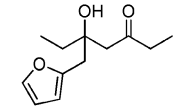
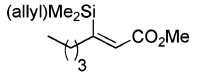
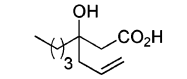
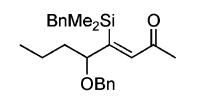
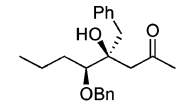
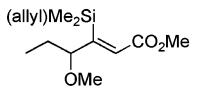
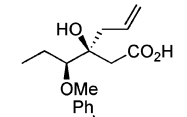
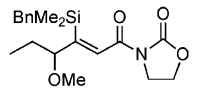
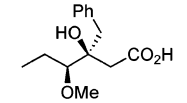
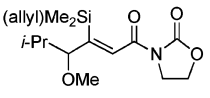
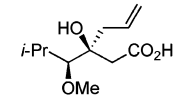
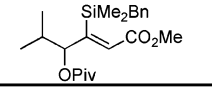
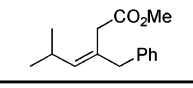

[a] Conditions: (a) TBAF in DMF, 0 °C to room temperature, 15 min. (b) 1.0M aq NaOH, room temperature, 2 h. (c) 30% aq $H_2O_2$, heat, 12 h. (d) $KHCO_3$, 30% aq $H_2O_2$, heat, 12 h.

silane oxidations,[7] and reports of tertiary silane oxidations are rare.[8] Attempts to oxidize silane **8**, either upon its isolation as a mixture (X = OH, $OSiR_3$, F) or in the same pot as the migration from **7**, were discouraging. Less than 50% conversion was observed even at rather high temperatures (120 °C). More forcing conditions resulted in decomposition.[9]

Surprisingly, a switch to ketone substrate **10** improved the situation dramatically. Direct treatment of the reaction mixture from the migration of **10** with aqueous hydrogen peroxide and heating to 80 °C resulted in clean formation of $\beta$-hydroxy ketone **12** (79% yield). Although the differing results with ketone and ester substituents on intermediates such as **8** were initially perplexing, we postulated that intramolecular five-membered ring siloxane formation from a hydrated ketone structure (**11**) might be responsible for the greatly improved oxidation efficiency. Intramolecular activation of silanes with a neighboring hydroxyl group capable of forming four- or five-membered ring siloxanes is known for several processes.[7,10] However, there is no strong evidence for such effects by other functional groups. We proposed that carboxylates (**14**) might have a similar effect. In fact, treatment of **13** with the migration conditions, followed by aqueous sodium hydroxide to induce saponification and finally hydrogen peroxide with heating, provided in a one-pot operation the desired $\beta$-hydroxyl acid **15** (83% yield).

We found that a variety of groups—phenyl, benzyl, 2-furanylmethyl, and allyl—on (*Z*)-$\beta$-silyl enones and enoates, upon treatment with TBAF in anhydrous polar solvents, undergo a 1,2-migration from silicon to carbon to form tertiary silanes in 5 min at 0 °C. Methyl groups on silicon are not transferred. It is not possible from the groups we have studied to determine whether the transferable groups serve to stabilize an anionic species acting as a nucleophile or a cationic three-centered transition state. Inorganic fluoride salts such as CsF and KF are far less effective even when some water is added to the reaction. The (*Z*)-$\beta$-silyl-enones and enoates (**4**) are also stable to "buffered" fluoride sources (HF, HF·pyrine, or 1:1 TBAF/AcOH mixtures) important for the removal of silyl ether protecting groups. Such transfers have been noted for terminal vinylsilanes, producing secondary silane products,[11] and in one case oxidation of a product from allyl transfer allowed access to a secondary alcohol.[12] In line with these reports, transfer of a phenyl group, which produces a benzylic silane intermediate, results in rapid protodesilylation under the migration conditions (Table 1, entry 1). The other groups used here produce very stable silane

***Table 2.*** Geminal Alkylation–Hydroxylation of Alkynyl Carbonyl Compounds

| entry | vinylsilane | cond.[a] | major product | Yield | dr |
|---|---|---|---|---|---|
| 1 |  | **D** |  | n.d. | |
| 2 |  | **A** |  | 75 | |
| 3 |  | **A** |  | 86 | |
| 4 |  | **A** |  | 81 | |
| 5 |  | **A** |  | 77 | |
| 6 |  | **B** |  | 67 | |
| 7 |  | **A** |  | 74 | 10:1 |
| 8 |  | **B** |  | 81 | 3:1 |
| 9 |  | **C** |  | 74 | >20:1 |
| 10 |  | **C** |  | 80 | >20:1 |
| 11 |  | **D** |  | 79 | 12:1 (*Z*:*E*) |

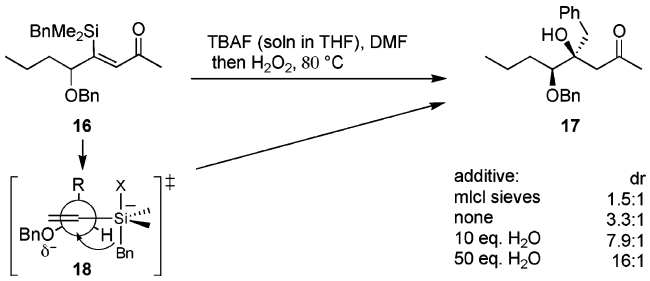
[a] Conditions. **A**: (i) 3 equiv of TBAF (1 M in THF) in DMF, 0 °C to room temperature, 15 min. (ii) 30% aq $H_2O_2$, heat to 80 °C, 8h. **B**: (i) 3 equiv of TBAF (1 M in THF) in DMF, 0 °C to room temperature, 15 min. (ii) 1 N aq NaOH, room temperature, 2h. (iii) $KHCO_3$, 30% aq $H_2O_2$, heat to 80 °C, 8h. **C**: (i) 3 equiv of TBAF (1M in THF) in 10:1 DMF/$H_2O$, 0 °C to room temperature, 2 h. (ii) 1 N aq NaOH, room temperature, 2h. (iii) $KHCO_3$, 30% aq $H_2O_2$, heat to 80 °C, 8h. **D**: 3 equiv of TBAF (1 M in THF) in DMF, 0 °C to room temperature, 15 min.

intermediates in near quantitative yield. The success of a 2-furanylmethylsilane (Table 1, entry 5) suggests that a wide variety of tethered "nucleophiles" are tolerated, including those for which employing a traditional organometallic anion is difficult. The intermediates can be isolated, but usually are mixtures of silanols and disiloxanes. To investigate the possibility that carbonyl coordination to the silyl group promotes the migration step, we synthesized isomeric terminal vinylsilanes, but reaction efficiency and rate were indistinguishable, indicating that coordination is not an important contribution to reactivity (Table 2, entries 2 and 3).

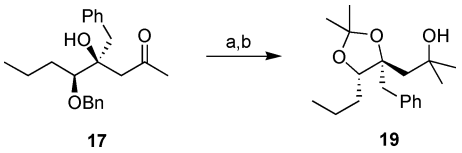
We were interested in studying the diastereoselectivity of migration for substrates with $\gamma$-chiral centers. Because propargylic alcohols are one of the synthons most readily amenable to asymmetric synthesis,[13] we were intrigued by the prospect that $\gamma$-alkoxy or $\gamma$-acyloxy substituents might serve as useful diastereo-directing groups to provide access to highly functionalized product structures. We were encouraged to find that a $\gamma$-benzyloxy ketone substrate (Table 2, entry 7) gives the expected clean conversion to a tertiary alcohol with significant control of diastereoselectivity (74%, 10:1 dr).

However, experiments with additional substrates were found to be irreproducible, especially with respect to diastereoselectivity,

***Scheme 3.*** Effect of Water on Diastereoselectivity




***Scheme 4.*** Determination of Product Diastereoselectivity[a]




[a] Conditions: (a) MeMgCl, THF, 67%. (b) $Pd(OH)_2/H_2$, then dimethoxypropane, PPTS, DMF, 52%.

and we reexamined the migration conditions. After excluding several other factors, we found a remarkable dependence of diastereoselectivity on the water content of the reaction medium (see Scheme 3). Varying the water content altered the diastereomeric ratio by 1 order of magnitude, from 1.5:1 (with 4 Å molecular sieves; in this case the reaction yield was considerably lower) to 16:1 (with 50 equiv of water added, amounting to a 10:1 DMF/water mixture). Adding water did increase reaction times somewhat (1−2 h), but complete conversion and high isolated yields were maintained. The extension of diastereoselective processes to ester substrates was generally disappointing. In some cases very modest selectivity could be obtained (Table 2, entry 8), while in others protodesilylation competed with 1,2-migration, providing (*E*)-enone and enoate byproducts. However, a change in acid derivatives to acyl oxazolidinones remedied both of these problems, and excellent yield and control of relative stereochemistry could be obtained (Table 2, entries 9 and 10).[14]

At present, the best model to explain the origins of diastereoselection appears to be silicate **18** (Scheme 3), which best minimizes both steric strain and charge-dipole interactions. The coordination number at silicon during the migration (5 vs 6) is one unknown that may have significant impact on the transition-state structure. As depicted here for a pentacoordinate silicon, the transferring group (Bn) would likely lie in an apical position, with a fluoride or hydroxide[15] occupying the other apical position to facilitate bond migration.

To establish the relative stereochemistry of the products from diastereoselective processes, the $\gamma$-benzyloxy ketone product (Table 2, entry 6) was converted to the cyclic acetonide **19** (Scheme 4). The relative stereochemistry was then determined through the use of nOe analysis. The identity of other diastereomeric products cases is assumed by analogy.

Vinylsilane substrates with $\gamma$-acyloxy substituents are also substrates for the Si → C migration, though in this case a facile elimination of the intermediate $\beta$-acyloxy silane occurs to provide the $\beta,\gamma$-unsaturated ester product (Table 2, entry 11). Good control of olefin geometry (12:1) is seen, with the favored isomer consistent with a trans elimination from the same diastereomeric intermediate observed in $\gamma$-alkoxy substrates. Control of trisubstituted olefin geometry in the formation of a sensitive $\beta,\gamma$-unsaturated ester product is noteworthy.

In summary, the regioselective alkyne hydrosilylation by a trans addition process, together with a one-pot C−C bond formation by Si → C migration and subsequent silane oxidation, provides a new strategy for the synthesis of $\beta$-carbonyl-substituted tertiary alcohols. The importance of neighboring ketone and carboxylate groups in promoting the oxidation of highly hindered tertiary silanes, an observation that may affect synthetic design of routes depending on such oxidations, was demonstrated.

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**Supporting Information Available:** Characterization data for all compounds, detailed experimental procedures, and details for the synthesis of substrates (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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