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Use of an Aminosilyllithium for the Diastereoselective Synthesis of Diphenyl Oxasilacyclopentane Acetals and Polyols

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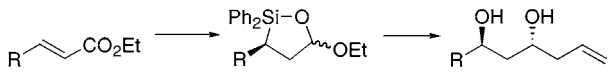
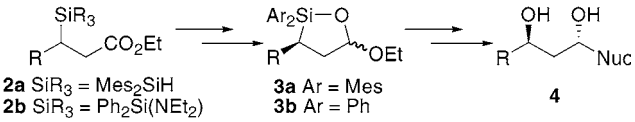
ABSTRACT



The conjugate addition reaction of a stable, in situ generated silyllithium gives a β-hydroxysilyl ester with high diastereoselectivity. Conversion of the β-hydroxysilyl ester to a β-fluorosilyl ester affords the precursor to the oxasilacyclopentane acetal in high yields under mild conditions. A hydride reduction and subsequent intramolecular silylation lead to the acetal in excellent yields. Finally, highly selective nucleophilic substitution affords oxasilacyclopentanes, which undergo a mild oxidation to afford 1,3-trans diols with high selectivity.

Oxasilacyclopentanes are powerful intermediates in organic synthesis, since they can be readily converted into diols after oxidation of the carbon−silicon bond.[1−13] Recently, we showed that a variety of highly functionalized 1,3-diols can be obtained diastereoselectively from α,β-unsaturated esters through the intermediacy of a dimesityl silacyclopentane acetal (Scheme 1).[14] Conjugate addition of $Mes_2HSiLi\cdot(THF)_2$ (**1**) to an α,β-unsaturated ester provided β-silyl ester **2a**, which underwent fluoride-catalyzed intramolecular hydrosilylation[15] of the carbonyl to afford acetal **3a**. Subsequent Lewis acid mediated nucleophilic substitution and oxidation of the carbon−silicon bond gave the 1,3-trans diol **4**.

Scheme 1. Formation of Polyols from β-Silyl Esters



Although high selectivities and yields were observed for this reaction sequence, we wanted to increase its efficiency and substrate compatibility. Hydrosilyllithium **1** is unstable in solution, so isolation of this anion as its stable THF solvate in a glovebox or using Schlenk techniques were required to obtain reliable yields.[16] The dimesitylsilyl anion would not add to (*Z*)-α,β-unsaturated esters. The steric bulk of the mesityl substituents on the silicon atom also required the

(1) Tamao, K.; Akita, M.; Kumada, M. *J. Organomet. Chem.* **1983**, *254*, 13−22.
(2) Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599−7662.
(3) Liu, D.; Kozmin, S. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4757−4759.
(4) Liu, D.; Kozmin, S. A. *Org. Lett.* **2002**, *4*, 3005−3007.
(5) Bols, M.; Skrydstrup, T. *Chem. Rev.* **1995**, *95*, 1253−1277.
(6) Murakami, M.; Suginome, M.; Fujimoto, K.; Nakamura, H.; Andersson, P. G.; Ito, Y. *J. Am. Chem. Soc.* **1993**, *115*, 6487−6498.
(7) Young, D. G. J.; Hale, M. R.; Hoveyda, A. H. *Tetrahedron Lett.* **1996**, *37*, 827−830.
(8) Hale, M. R.; Hoveyda, A. H. *J. Org. Chem.* **1994**, *59*, 4370−4374.
(9) Zacuto, M. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 8587−8588.
(10) Zacuto, M. J.; O'Malley, S. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7890−7891.
(11) Tamao, K.; Nakajima, T.; Sumiya, R.; Arai, H.; Higuchi, N.; Ito, Y. *J. Am. Chem. Soc.* **1986**, *108*, 6090−6093.
(12) Kablean, S. N.; Marsden, S. P.; Craig, A. M. *Tetrahedron Lett.* **1998**, *39*, 5109−5112.
(13) Tanino, K.; Yoshitani, N.; Moriyama, F.; Kuwajima, I. *J. Org. Chem.* **1997**, *62*, 4206−4207.
(14) Powell, S. A.; Tenenbaum, J. M.; Woerpel, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 12648−12649.
(15) Davis, A. P.; Hegarty, S. C. *J. Am. Chem. Soc.* **1992**, *114*, 2745−2746.
(16) Roddick, D. M.; Heyn, R. H.; Tilley, T. D. *Organometallics* **1989**, *8*, 324−330.

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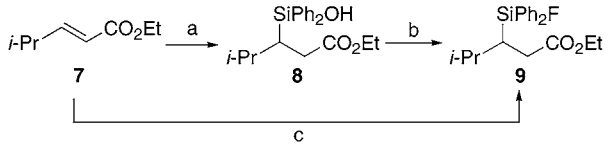
Scheme 2. Conjugate Addition to Ester **7**[a]



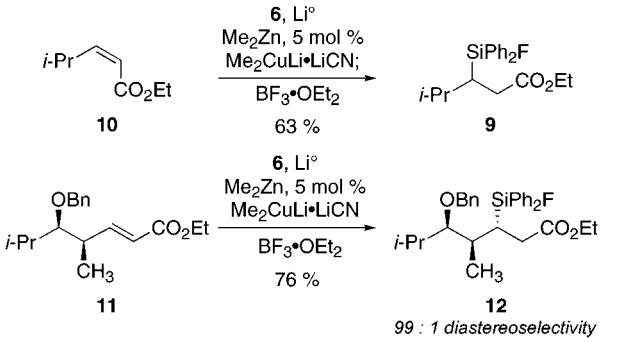
[a] Reaction conditions: (a) (i) **6**, Li^0; then Me_2Zn, 5 mol % $Me_2CuLi{\cdot}LiCN$; (ii) aqueous NH_4Cl, 68%. (b) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C, 78%. (c) Conditions as in (a) and (b), but without isolation of silanol **8**; 68% over two steps.

use of strongly basic conditions to oxidize the oxasilacyclopentane.

This communication reports the development of methodology that greatly improves the sequence shown in Scheme 1. The aminosilyllithium $Ph_2Si(NEt_2)Li$ (**5**) developed by Tamao and Kawachi was used to introduce the carbon−silicon bond, obviating the isolation of an unstable silyllithium.[17−19] Because metal-mediated conjugate addition of silyl anion **5** led to a β-silyl ester lacking a hydride functionality[20] (as compared to the original protocol), conversion of ester **2** to acetal **3** was re-engineered. The resulting oxasilacyclopentane was oxidized easily under mild Tamao conditions.[21] This new procedure allows for the diastereoselective synthesis of polyols from both (*E*)- and (*Z*)-enoates.

The conversion of the α,β-unsaturated ester to the appropriately functionalized β-silyl ester was accomplished in two steps. The metal-mediated conjugate addition[22,23] of aminosilyllithium **5**, generated in situ from $Ph_2Si(NEt_2)Cl$ (**6**),[24] to α,β-unsaturated ester **7** followed by aqueous workup afforded β-hydroxysilyl ester **8** in 68% yield (Scheme 2).[17] Treatment of hydroxysilyl **8** with $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at −78 °C gave β-fluorosilyl ester **9** in 78% yield.[25] Harsh conditions, such as HF or $Ph_2S(O)F_2$, were previously required to convert silanols to fluorosilanes.[26−30] Further optimization was achieved, because conversion of enoate **7** to ester **9** could be carried out with only a single purification, resulting in a 68% overall yield.

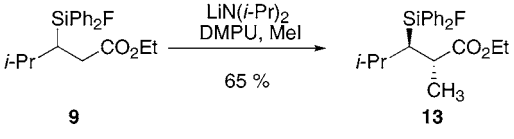
Scheme 3. Conjugate Addition to Esters **10** and **11**



These conditions were applied to a variety of other substrates. Metal-mediated conjugate addition to (*Z*)-enoates, which were unreactive with silyllithium **1**,[14] could now be performed with $Ph_2Si(NEt_2)Li$ (**5**). Metal-mediated conjugate addition of aminosilyllithium **5** to enoate **10** and subsequent treatment of the silanol with $BF_3{\cdot}Et_2O$ afforded a 63% overall yield of β-fluorosilyl ester **9** (Scheme 3). The metal-mediated conjugate addition of aminosilyllithium **5** to enoates containing stereogenic centers proceeded with high selectivity.[8,31,32] Addition of $Ph_2Si(NEt_2)Li$ (**5**) to enoate **11** followed by conversion to the fluoride afforded ester **12** with a 99:1 diastereoselectivity in 76% overall yield (Scheme 3).

The enolate of the β-fluorosilyl ester could be alkylated without *O*-silylation of the fluorosilane. Treatment of ester **9** with $LiN(i\text{-}Pr)_2$, 5 equiv of DMPU, and 2 equiv of MeI at −78 °C gave β-fluorosilyl ester **13** with 90:10 diastereoselectivity in 65% yield (Scheme 4).[33] Upon warming the

Scheme 4. Diastereoselective Addition to Ester **9**

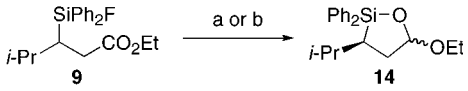


enolate above −78 °C, significant amounts of *O*-silylation were observed.

With the β-fluorosilyl esters in hand, a variety of hydride reducing agents were screened for the hydride reduction and subsequent intramolecular silylation reaction. The use of mild reducing agents resulted in no reaction with ester **9**, and strong reducing agents led to hydrolysis of the fluorosilane. Treatment with $i\text{-}Bu_2AlH$ in CH_2Cl_2 at −78 °C provided a β-fluorosilyl aldehyde, which afforded a mixture of the methyl and ethyl oxasilacyclopentane acetals upon addition

(17) Tamao, K.; Kawachi, A.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 3989−3990.
(18) Usuda, H.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 3621−3624.
(19) Barrett, A. G. M.; Head, J.; Smith, M. L.; Stock, N. S.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **1999**, *64*, 6005−6018.
(20) Diphenylhydrosilyllithium is unstable and gave irreproducible results.
(21) Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M. *Organometallics* **1983**, *2*, 1694−1696.
(22) Lipshutz, B. H.; Sclafani, J. A.; Takanami, T. *J. Am. Chem. Soc.* **1998**, *120*, 4021−4022.
(23) Ager, D. J.; Fleming, I.; Patel, S. K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2520−2526.
(24) Chlorosilane **6** can be easily synthesized on a multigram scale. Tamao, K.; Nakajo, E.; Ito, Y. *Tetrahedron* **1988**, *44*, 3997−4007.
(25) Despite the additional steps, the formation of the β-fluorosilyl ester was necessary as hydride reduction of the β-aminosilyl or β-silanol esters led only to β-silyl aldehydes.
(26) Ou, X.; Janzen, A. F. *J. Fluorine Chem.* **2000**, *101*, 279−284.
(27) Earborn, C. *J. Chem. Soc.* **1953**, 494−497.
(28) Earborn, C. *J. Chem. Soc.* **1952**, 2846−2848.
(29) Handy, C. J.; Lam, Y.-F.; DeShong, P. *J. Org. Chem.* **2000**, *65*, 3542−3543.
(30) Magar, S. S.; Desai, R. C.; Fuchs, P. L. *J. Org. Chem.* **1992**, *57*, 5360−5369.
(31) Krief, A.; Provins, L.; Dumont, W. *Angew. Chem., Int. Ed.* **1999**, *38*, 1946−1948.
(32) Yamamoto, Y.; Chounan, Y.; Nishii, S.; Ibuka, T.; Kitahara, H. *J. Am. Chem. Soc.* **1992**, *114*, 7652−7660.
(33) McGarvey, G. J.; Williams, J. M. *J. Am. Chem. Soc.* **1985**, *107*, 1435−1437.

Scheme 5. Hydride Reduction and Intramolecular Silylation of Ester **9**[a]

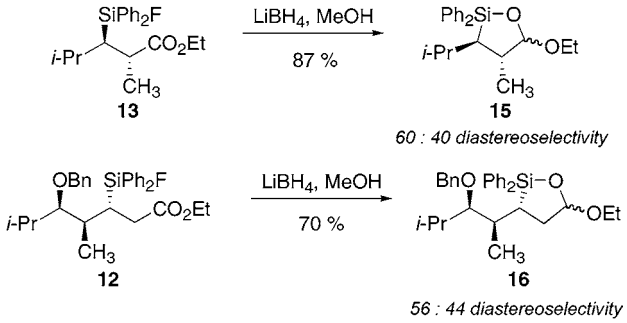


[a] Reaction conditions: (a) (i) *i*-Bu_2AlH, CH_2Cl_2, −78 °C; (ii) EtOH, 97%, 68:32 ds. (b) 1:1 $LiBH_4$/MeOH, Et_2O, 22 °C, 86%, 56:44 ds.

of MeOH. When the aldehyde was treated with EtOH, the desired ethyl acetal **14** was obtained as a 62:38 ratio of acetal epimers in 97% yield (Scheme 5).[34] The reduction with *i*-Bu_2-AlH was sensitive to the reaction conditions, and even small variations in temperature or concentration led to significant amounts of overreduction of the ester. Treatment of ester **9** with $LiBH_4$ and MeOH in Et_2O at 22 °C resulted in the direct formation of oxasilacyclopentane acetal **14** as a 56:44 mixture of acetal epimers in 86% yield without formation of the β-fluorosilyl aldehyde or significant amounts of overreduction.

With optimized conditions in hand, the procedure was applied to the other β-fluorosilyl esters to afford oxasilacyclopentane acetals **18** and **19** in good yield (Scheme 6). The

Scheme 6. Hydride Reduction and Intramolecular Silylation of Esters **12** and **13**

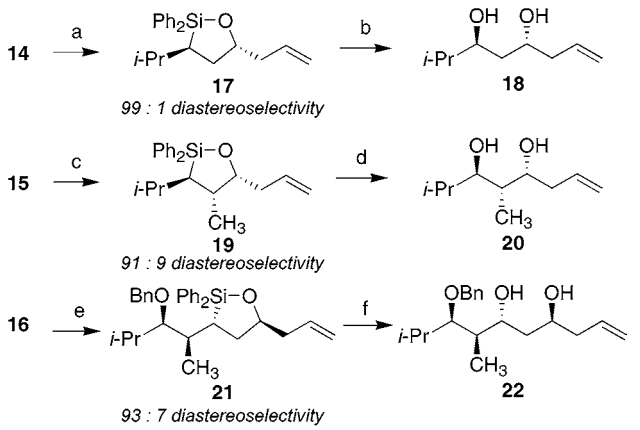


use of $LiBH_4$ and MeOH resulted in direct silylation of esters **15** and **16** with little or no overreduction observed. The direct formation of the acetal using $LiBH_4$ was employed to avoid the concern that acetal formation could be incomplete with the two-step *i*-Bu_2AlH procedure.

As in the case with the mesityl-substituted oxasilacyclopentane acetals,[14] Lewis acid mediated nucleophilic substitution of allyltrimethylsilane followed by oxidation of the carbon−silicon bond proceeded with excellent selectivities for acetals **14**−**16** (Scheme 7). The observed selectivities are in accordance with our studies of five-membered-ring oxocarbenium ions.[35] Oxidation of the oxasilacyclopentanes **17**, **19**, and **21** to polyols **18**, **20**, and **22** was performed with the more mild Tamao conditions, which illustrated the

(34) The reduction could also be carried out in toluene, but the yields were lower.

Scheme 7. Conversion of Acetals **14**−**16** to 1,3-Diols **18**, **20**, and **22**[a]



[a] Reaction conditions: (a) $CH_2CHCH_2Si(CH_3)_3$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 85%. (b) 30% H_2O_2, KF, $KHCO_3$, 1:1 MeOH/THF, 64%. (c) $CH_2CHCH_2Si(CH_3)_3$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 63%. (d) 30% H_2O_2, KF, $KHCO_3$, 1:1 MeOH/THF, 62%. (e) $CH_2CHCH_2Si(CH_3)_3$, $SnCl_4$, toluene. (f) 30% H_2O_2, KF, $KHCO_3$, 1:1 MeOH/THF, 56% over two steps.

functional group tolerance of the overall reaction sequence (Scheme 7).[1,2,21,36]

In conclusion, we have developed a method for the synthesis of oxasilacyclopentane acetals, which serve as valuable precursors for the diastereoselective synthesis of 1,3-trans diols. The conjugate addition reaction of a stable, in situ generated silyllithium proceeded with high diastereoselectivity. Conversion of a β-hydroxysilyl ester to a β-fluorosilyl ester afforded the precursor to the hydride reduction reaction in high yields under mild conditions. The reduction and subsequent intramolecular silylation led to the oxasilacyclopentane acetal in excellent yields using a variety of mild reducing agents. Finally, highly selective nucleophilic substitution afforded oxasilacyclopentanes, which underwent a mild Tamao oxidation[21] of the carbon−silicon bond to provide 1,3-trans diols with high selectivity.

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Supporting Information Available: Full experimental procedures and spectroscopic proof of stereochemistry. This material is available free of charge via the Internet at http://pubs.acs.org.

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(35) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12209−12210.

(36) The nucleophilic substitution and oxidation reactions have not been optimized, and an erosion in the yields were observed compared to reactions with the dimesityloxasilacyclopentane acetals.