# Tritylallyldimethylsilane−TiCl₄ Annulations to Electron Deficient Olefins. Diastereomerically Pure 3-Substituted and 3,4-Disubstituted Cyclopentanols

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The Lewis acid mediated additions of allylsilanes to electron deficient alkenes has proven to be a powerful method for the preparation of cycloalkanes.[1] We have recently demonstrated this annulation method in the preparation of both kinetic (2 + 2) and thermodynamic (3 + 2) addition products from chiral bicyclic systems **1** (Scheme 1).[1j] It was our intention to further transform adducts **3**, to chiral cyclopentanols **4**, for use in more complex synthetic schemes.[2] Unfortunately, this goal depended heavily on replacement of the silicon moiety with a hydroxyl group. To date, all known oxidizable silanes require that they possess at least one "activating" group (H, N, O, Hal, aryl) in order to cleave the C−Si bond,[3] the most commonly used in this regard possessing the dimethylphenyl substituents.[4] In the present case, the allylsilane cycloadditions (Scheme 1) require that the substituents on silicon be sterically demanding[1a−h] (e.g. isopropyl) in order to avoid Sakurai products.[5] Thus, it became critical that new, sterically encumbered, silicon-labile substituents be found. For example, **3** contains silicon bound to four alkyl groups and would resist C−Si cleavage to furnish the carbinol. A recent report by Knölker[6] nicely demonstrated how the triphenylsilyl group could be oxidatively traded for a hydroxyl, which has now prompted us to report our results of, and further solutions to, this important synthetic problem. We initially utilized chiral lactams **1** (R = Ph, R¹ = *t*-Bu) with diphenylmethyl- and triphenylallylsilanes and found little or no cycloaddition products due to the unreactive nature of these allylsilanes.[7] We learned, in this particular case, that *at least two* alkyl substituents on silicon were necessary if addition to the lactams was to proceed. Furthermore, if bulky substituents (e.g. *i*-Pr, cyclohexyl) were affixed to the silicon, then the Sakurai products were precluded, yet oxidative removal of the silyl moiety was not possible. This delicate balance between reactivity and silicon removal was fortunately achieved by use

Scheme 1

Scheme 2
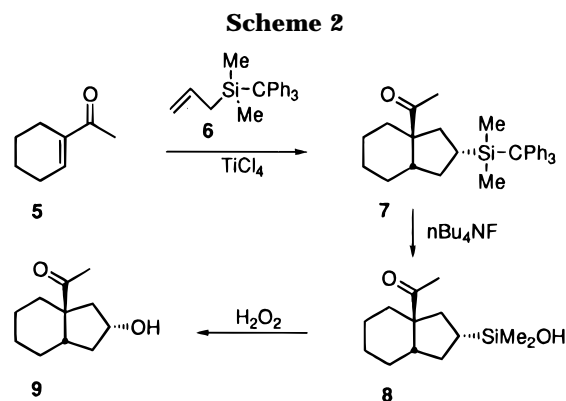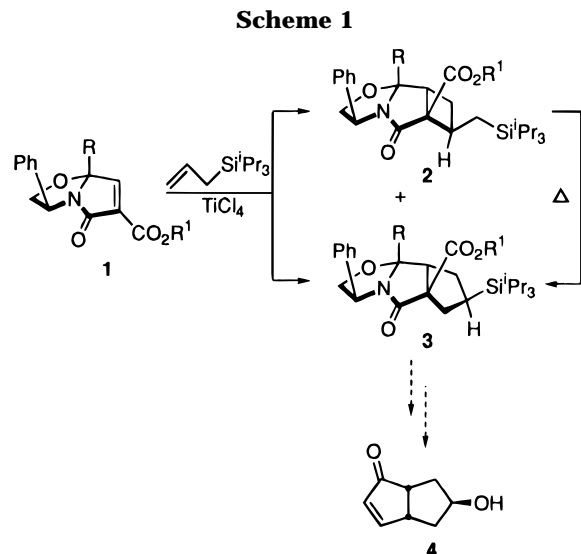
of the trityldimethylsilyl group.[8] The large trityl group, the necessary alkyl groups, and the potential ease of removal of the Si−CPh₃ link augered well for a successful solution to the problem.

We now report that cycloadditions of tritylallyldimethylsilane **6** to electron poor olefins proceed in good yield and, more significantly, oxidative removal of the silicon moiety proceeds under mild, nonepimerizing conditions (*vide infra*).

Thus, addition of **6** to a precomplexed mixture of 1-acetylcyclohexene **5** and titanium tetrachloride in dry CH₂Cl₂ at 0 °C afforded, after warming to 10 °C, cycloadduct **7** as a single diastereomer in 80−85% yield (Scheme 2). Addition of tetrabutylammonium fluoride (THF, 0 °C) then resulted in rapid expulsion of the trityl group producing silanol **8**. Treatment with KHCO₃, methanol, and hydrogen peroxide[3] gave, after several hours of vigorous stirring at room temperature, the bicyclic keto alcohol **9** as a single compound (67%).[9]

The overall yield for the two-pot sequence **5** → **9** was 55% and was shown to be general. Thus additions to chiral lactams **1** gave either cyclobutane or cyclopentane

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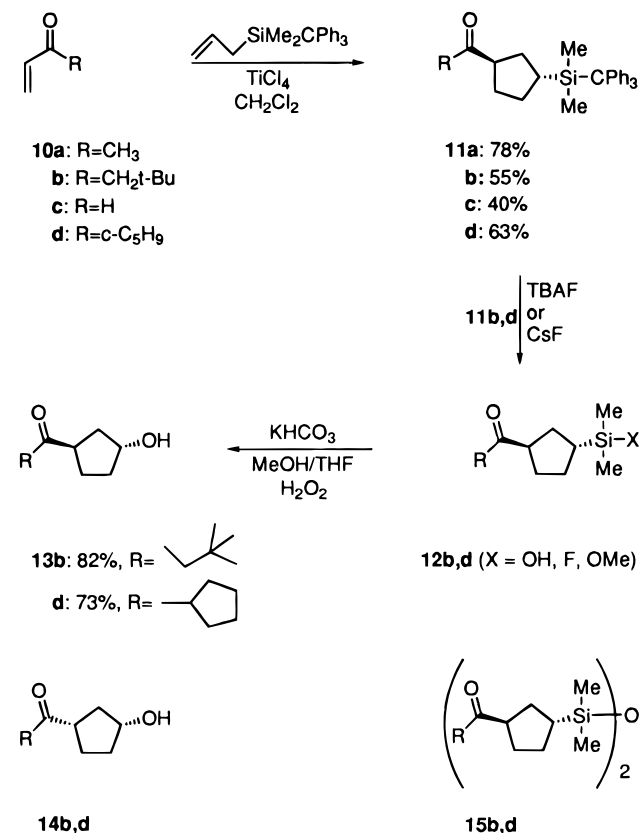
(2) Romo, D.; Meyers, A. I. *Tetrahedron* **1991,** *47,* 9503.

(3) Tamao, K.; Ishida, N. *J. Organomet. Chem.* **1984,** *269,* C37.

(4) Fleming, I.; Henning, R.; Parker, D. C.; Plaut, H. E.; Sanderson, P. E. J. *J. Chem. Soc., Perkin Trans. 1* **1995,** 317 and references cited therein.

(5) Review: Hosomi, A. *Acc. Chem. Res.* **1988,** *21,* 200.

(6) Knolker, H.-J.; Wanzyl, G. *Synlett* **1995,** 378.

(7) Mayr, H.; Patz, M. *Angew. Chem., Int. Ed. Engl.* **1994,** *33,* 938. The phenyl groups act as electron-withdrawing substituents and significantly reduce the reactivity of the allyl group.

(8) Ager, D. J.; Fleming, I. *J. Chem. Res. (S)* **1977,** 6.

(9) The diastereomeric purity of all cycloadducts was judged to be ≥97:3 by ¹H NMR. The relative stereochemistry depicted was not rigorously determined, rather it was based on substantial literature precedence for the electron-withdrawing group adopting a *trans* relationship to the bulky silyl substituent (see references 1a−g). Because the oxidation is known to occur with complete retention of configuration, the relative stereochemistry of the cyclopentanol products is presumed to be *trans* as well. Furthermore, the spectral data (¹H and ¹³C NMR) obtained for bicyclic keto alcohol **9** compare well with those reported by Knolker (see reference 6).

Scheme 3

10a: R=CH₃
b: R=CH₂t-Bu
c: R=H
d: R=c-C₅H₉

11a: 78%
b: 55%
c: 40%
d: 63%

13b: 82%, R=
d: 73%, R=

12b,d (X = OH, F, OMe)

14b,d

15b,d

cycloadducts, while additions to alkynyl esters gave cyclobutene adducts.[1j,10]

It soon became obvious that an important stereochemical question be addressed concerning the effect of the Si–C cleavage on any epimerizable carbonyl system. It can be seen that bicyclic ketone **7** cannot epimerize due to the absence of an enolizable proton, thus the sequence **7 → 9** does not appropriately address this question. However, alkenes such as **10** would test the efficacy of this procedure if the cyclic adducts **11** could be transformed into the stereochemically pure carbinols, **13**. Addition of tritylsilane **6** to electron poor olefins **10a–d**, in the presence of TiCl₄, gave cyclopentanes **11a–d** in 40–78% yield as single diastereomers (Scheme 3).[9] These products, upon silicon cleavage, were then evaluated for their resistance to epimerization. It turned out that the enolization of **11**, en route to **13**, was highly dependent on the method employed for protodesilylation.

The replacement of silicon by a hydroxy group is known to occur with complete stereochemical retention[4] yet the

conditions to affect this important transformation may readily cause enolization of any labile α-protons. For example, when **11b** was treated with aqueous TBAF in THF at 0 °C,[11] silane **12** (X = OH) was obtained, which afforded cyclopentanol **13b** in low yield (~40%) after oxidation. Furthermore, **13b** was obtained as a single diastereomer, presumably *trans*,[9] whereas a significant quantity (~40%) of the siloxane **15b** was also obtained. If the concentration of water was significantly reduced in the desilylation step, utilizing TBAF treated with sieves,[12] then the fluorosilane **12b** (X = F) was the only product formed. Unfortunately, oxidation of the latter using KHCO₃–MeOH–H₂O₂ yielded only a poor 1.2:1.0 ratio of **13b:14b**, respectively. We attribute this disappointing stereochemical result to epimerization by the trityl anion, which acted as a base. It therefore became clear that basic conditions must be avoided during the desilylation step. With this in mind, we found that optimum conditions to effect the desilylation and oxidation required pretreated TBAF,[12] or CsF,[13] in methanol–THF. In this fashion, **12b,d** (X = OMe) were readily formed which, after the oxidation step, afforded 3-substituted cyclopentanols **13b,d** in 70–80% yield with greater than 97% stereochemical purity.[14] Alternatively, a dry THF solution of **11b**, treated with 1–1.2 equiv of glacial acetic acid or benzoic acid, followed by 2.0 equiv of pretreated TBAF, also gave, after oxidation, pure **13b** in 60–70% yield. No evidence of the epimers **14**, or siloxanes **15**, was observed under either set of conditions. As expected, however, when pure **13b** and **13d** were subjected to sodium methoxide in methanol for several hours, epimerization was clearly observed (approximately a 1.5:1.0 ratio of **13:14** could readily be detected in the ¹H NMR spectrum for both **b** and **d**).

In summary, we have demonstrated that tritylaldimethylsilane **6** is a mild and efficient reagent for effecting a net 2-hydroxypropyl annulation to electron deficient alkenes. Furthermore, sensitive, enolizable cyclopentane derivatives do not appear to lose their stereochemical integrity during the process.

Supporting Information Available: Detailed experimental procedures, physical data, and ¹H and ¹³C-NMR for all new compounds (36 pages).

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(10) The full scope of cycloaddition reactions with **6**, including the formation and utilization of tricyclic lactams **i** and **ii**, will be the subject of a future publication.
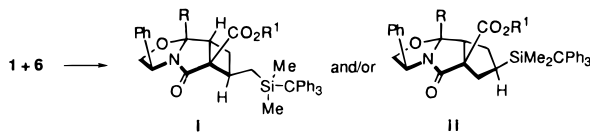
(11) Tetrabutylammonium fluoride (TBAF) purchased from Aldrich as 1.0 M in THF contains 5 wt % water (or 2.5 M H₂O).

(12) Commercially available tetrabutylammonium fluoride (1.0 M in THF) can be sufficiently dried immediately prior to use by stirring 2–3 h over 3 Å sieves.

(13) Anhydrous cesium fluoride is prepared by heating the solid in the reaction vessel, under vacuum, with a heat gun for several minutes.

(14) Cyclopentanols **13b,d** and epimers **14b,d** are readily distinguishable in the ¹H NMR spectrum. Careful examination of the protons at the hydroxy carbons (≈4.3–4.4 ppm) in **13** showed <3% of the epimers **14**.