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[2 + 2] and [3 + 2] Cycloadditions of Triisopropylallylsilane to α,β-Unsaturated Bicyclic Lactams[†]

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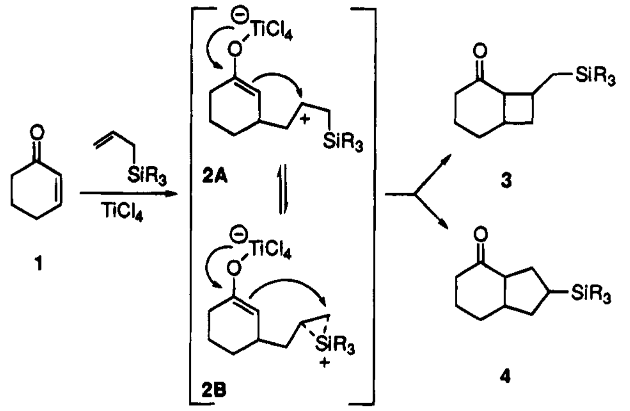
Summary: Addition of allylsilane gave cyclobutanes at low temperature and cyclopentanes at higher temperature.

The Lewis acid mediated [3 + 2] cycloaddition of allylsilanes to α,β-unsaturated carbonyl compounds, giving silyl-substituted cyclopentanes, has been an area of considerable interest in the recent literature.[1a−j] The process is believed to involve a conjugate addition of the silyl π-system to the α,β-unsaturated carbonyl, e.g., **1**, resulting in the intermediate silicon stabilized delocalized cation, **2A,B** (Scheme 1). The latter is then poised to cyclize at either of two available sites. Recent studies have demonstrated that alkylation occurs exclusively at the less substituted (terminal) carbon forming the cyclopentane derivative **4**, which also represents a net 1,2-shift by the silyl group. The formation of cyclobutane products **3**, resulting from attack at the more substituted (internal) carbon (Scheme 1), had been reported earlier as byproducts in several Sakurai reactions.[1a,2a−f] However, Knölker[1b,c] has recently shown that the majority of these reported [2 + 2] adducts were incorrectly assigned, and it was more likely that these were all actually cyclopentane derivatives. Thus, to date, it was believed that no true cyclobutanes had yet been obtained from the addition of allylsilanes to electrophilic olefins.[3]

Scheme 1



In the course of examining Lewis acid mediated additions of various silanes to unsaturated chiral lactams **5**, very poor yields of the expected cyclopentane-fused lactams **7** were formed, particularly when sterically small to moderate allylsilanes (e.g., $SiMe_3$, $SiMe_2Ph$) were employed (Scheme 2). The reactions proceeded very slowly in the case of electron deficient ($SiPh_3$, $SiPh_2Me$) silanes.[1i,5] Sakurai products (i.e., allyl addition) were the only other products formed, as was observed earlier.[1a,f] When the sterically endowed triisopropylallylsilane was employed, the cyclopentane-annulated products **7a−d** were obtained cleanly and in good yields (Table 1). This is in accordance with observations made by Danheiser and others[1a,f,j,4] wherein allenyl- and allyltriisopropylsilanes (allyl TIPS) were shown to lead to five-membered ring derivatives on addition to unsaturated ketones.

When the reaction of bicyclic lactam **5d** and allyl TIPS was subjected to closer scrutiny, it became apparent a product other than the cyclopentane was present and this could be isolated in fair to good yields. The amount of this product appeared to be the result of reaction conditions which varied with the temperature of the quenching step (aqueous saturated NH_4Cl). The new substance, obtained almost exclusively by quenching the addition of allyl TIPS to bicyclic lactam **5d** at −78 °C, was shown, by ^1H- and ^{13}C-NMR as well as confirmation by X-ray analysis, to be the cyclobutane product **6d**. Only a trace (<5%) was found to be the cyclopentane, **7d**. On the other hand, if the reaction of **5d** with allyl TIPS was quenched at 0 °C, only a trace of the cyclobutane **6d** was formed while the major product isolated (53%) was the expected cyclopentane, **7d**. From Table 1, it is seen that the low-temperature quench of allyl TIPS and several chiral bicyclic lactams **5a−d** gives the cyclobutane (entries 2, 4, 6, 8) while at higher temperatures the cyclopentane is essentially the only product formed (entries 1, 3, 5, 7).

Thus, in spite of evidence shown by Knölker[1c] that the earlier reports of cyclobutanes were in error, the pathway leading to cyclobutane products was indeed vindicated,

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[⊛] Abstract published in *Advance ACS Abstracts*, August 15, 1994.

(1) (a) Danheiser, R. L.; Dixon, B. R.; Gleason, R. W. *J. Org. Chem.* **1992**, *57*, 6094 and references cited therein. (b) Knölker, H.-J.; Jones, P. G.; Pannek, J. B. *Synlett* **1990**, 429. (c) Knölker, H.-J.; Graf, R. *Tetrahedron Lett.* **1993**, *34*, 4765 and references cited therein. (d) Panek, J. S.; Jain, N. F. *J. Org. Chem.* **1993**, *58*, 2345. (e) Knölker, H.-J.; Graf, R. *Synlett* **1994**, *19*, 131. (f) Knölker, H.-J.; Foitzik, N.; Goesmann, H.; Graf, R. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1081 and references cited therein. (g) For an example of allyltin additions to α,β-unsaturated iron acyl compounds, see: Herndon, J. W.; Wu, C.; Harp, J. J.; Kreutzer, K. A. *Synlett* **1991**, 1. (h) For examples of iron allyl additions to α,β-unsaturated carbonyl compounds, see: Chan, D. M. T. In *Comprehensive Organic Syntheses*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon: New York, 1991; Vol. 5. (i) Knölker, H.-J.; Foitzik, N.; Graf, R.; Pannek, J.-B. *Tetrahedron* **1993**, *49*, 9955. (j) Danheiser, R. L.; Takahashi, T.; Bertok, B.; Dixon, B. R. *Tetrahedron Lett.* **1993**, *34*, 3845 and references cited therein.

(2) (a) Hosomi, A.; Kobayashi, H.; Sakurai, H. *Tetrahedron Lett.* **1980**, *21*, 955. (b) Pardo, R.; Zahra, J. P.; Santelli, M. *Tetrahedron Lett.* **1979**, *20*, 4557. (c) Danishevsky, S.; Kahn, M. *Tetrahedron Lett.* **1981**, *22*, 485. (d) House, H. O.; Gaa, P. C.; VanDerveer, D. J. *J. Org. Chem.* **1983**, *48*, 1661. (e) Majetich, G.; Defauw, J.; Ringold, C. *J. Org. Chem.* **1988**, *53*, 50. (f) Nikisch, K.; Laurent, H. *Tetrahedron Lett.* **1988**, *29*, 1533.

(3) After this manuscript was completed, a report by Monti (*Tetrahedron Lett.* **1994**, *35*, 3073) reaffirmed their earlier work, questioned by Knölker (ref 1i above), that cyclobutanes were indeed formed in modest yields when allylsilanes were added to yne esters and ynones. (See also: Snider, B. B., et al. *J. Am. Chem. Soc.* **1979**, *101*, 5283.)

(4) (a) Danheiser, R. L.; Kwasigroch, C. A.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1985**, *107*, 7233. (b) Danheiser, R. L.; Becker, D. A. *Heterocycles* **1987**, *25*, 277. (c) Becker, D. A.; Danheiser, R. L. *J. Am. Chem. Soc.* **1989**, *111*, 389. (d) Danheiser, R. L.; Stoner, E. J.; Koyama, H.; Yamashita, D. S.; Klade, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 4407.

(5) Abel, E. W.; Rowley, R. J. *J. Organomet. Chem.* **1975**, *84*, 199. Dimethylphenylallylsilane and diphenylmethylallylsilane were prepared by the addition of allylmagnesium bromide to dimethylphenylsilyl chloride and diphenylmethylsilyl chloride, respectively.

0022-3263/94/1959-5144$04.50/0

Scheme 2

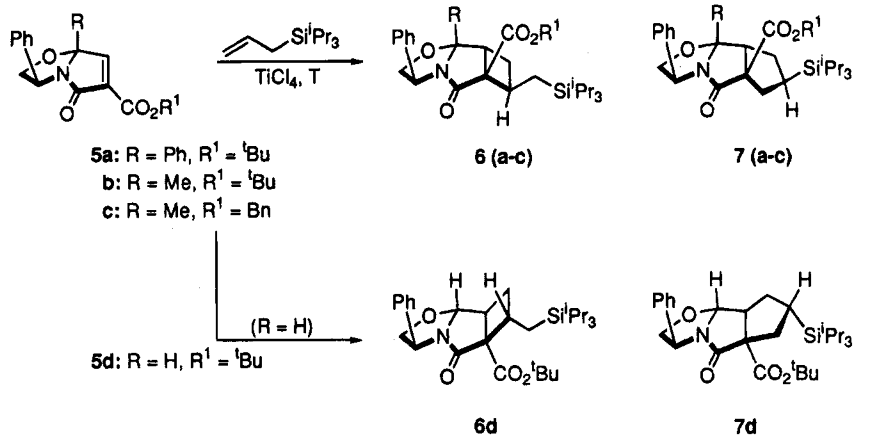


Table 1. Triisopropylallylsilane Addition to Unsaturated Lactams 5a–d[a]

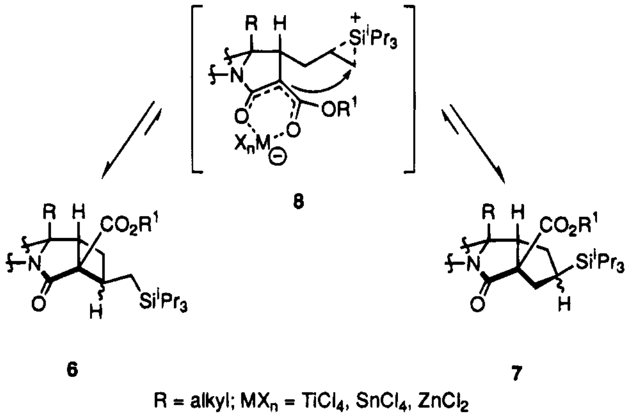
entry	compd	T (°C)	(%) **6**[b,d]	(%) **7**[b,d]
1	**5a**	−78 to 0	trace	68
2	**5a**	−78 to −20	60	trace
3	**5b**	−78 to −20	trace	68
4	**5b**	−78	70	10
5	**5c**	−78 to −20	trace	60
6	**5c**	−90	37[c]	trace
7	**5d**	−78 to 0	trace	53
8	**5d**	−78	63	trace

[a] All reactions were performed in anhydrous dichloromethane; 0.1 M in **5**. Entries 1, 2, 3, and 5: 1.1 equiv of allylsilane and 1.0 equiv of titanium tetrachloride were used. All other examples utilized 3.0 equiv of triisopropylallylsilane and 1.2 equiv of titanium tetrachloride. All reactions were performed by cooling a dichloromethane solution of **5** and silane to the initial temperature, adding the Lewis acid dropwise, and then warming the mixture slowly to the final temperature listed. The reactions were quenched with a saturated aqueous ammonium chloride solution. [b] All yields reported are isolated chemical yields, unless otherwise noted. [c] Chemical yield of **6** is based on 45% recovered starting material. [d] "Trace" refers to material detected *via* NMR and deemed to be below 5%.

at least in the particular α,β-unsaturated systems utilized herein. It was observed, however, that little or no cycloadditions ([2 + 2] or [3 + 2]) occurred if the ester group in **5** was absent. This limitation may require a stronger Lewis acid to induce allylsilane addition, and we are investigating this aspect further.

The experimental observations suggest that cyclobutanes **6a–d** are kinetic products whereas cyclopentane products **7a–7d** are thermodynamically controlled. In order to confirm this, the pure cyclobutane **6a** (R = Ph, R′ = *t*-Bu) was treated with titanium(IV) chloride at −78 °C and, upon warming, immediately rearranged to the corresponding cyclopentane derivative **7a**. Although other Lewis acids did indeed promote rearrangement of **6** to **7**, these were ineffective in catalyzing the addition of triisopropylallylsilane to **5**. Furthermore, the rate of rearrangement was shown to be dependent upon the Lewis acid strength (i.e., rate increases with strength of acid, $TiCl_4 > SnCl_4 > ZnCl_2$) (Scheme 3).

Scheme 3



From a stereochemical standpoint, the cycloadditions of triisopropylallylsilane to the unsaturated lactams **5** produced cyclobutanes **6** and cyclopentanes **7** containing three stereocenters. Adducts **6a–d** and **7a–d** have all been isolated as pure diastereomers after chromatography. Although the ratios have not been accurately assessed in the crude products containing **6** and **7** (NMR), there is little doubt that the selectivity of the cyclopentane and/or cyclobutane products is quite high. As for the absolute stereochemistry, only **6d** has been confirmed by X-ray analysis (*vide supra*).[9] The stereochemistry of other cyclobutyl adducts, containing either an angular phenyl or methyl substituent **6a** or **6b,c**, respectively, have not been subjected to X-ray analysis. However, on the basis of NMR studies and precedence,[6] cycloadditions to bicyclic lactams **5** possessing angular H were shown to proceed predominantly from the exo (β) face whereas those lactams containing an alkyl or aryl substituent **5a–c** all heavily favored endo (α) cycloaddition products. Thus, we can state, based upon the above, that cyclobutanes **6a–c** and cyclopentane adducts **7a–c** possess the endo stereochemistry. Furthermore, from NMR studies, the position of the silyl group in the [3 + 2] products, **7a–c**, appears to be β-disposed.[7] In the cyclobutane [2 + 2] products **6**, it was also feasible to determine the stereochemistry of the triisopropylmethyl group, using NOE studies.[7]

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[6] (a) Meyers, A. I.; Romo, D. *Tetrahedron* **1991**, *46*, 9503. (b) Meyers, A. I.; Snyder, L. B. *J. Org. Chem.* **1993**, *58*, 36.

[7] Two-dimensional C,H and H,H NMR correlation experiments were done for **6a** and **7a**. For the two compounds, the NMR is consistent with the proposed regiochemistry. Two-dimensional C,H correlation shows a methine carbon at δ 12 and δ 1.1 for **7a** and a methylene carbon at δ 13 and δ 0.8, 1.1 for **6a**. Two-dimensional H,H homonuclear correlation (COSY) is consistent with the C-H from **7a** sandwiched between two methylenes as in the proposed five-membered ring. COSY is also consistent with an exocyclic CH_2 in **6a** which is correlated only to a CH. This CH finds correlations to one other CH_2 as expected in the proposed four-membered ring. Both ^{13}C and ^1H chemical shifts of the CH and CH_2 in question are consistent with direct bonding to the Si functionality. $^3J_{HH}$ and/or NOE are also consistent with the silicon moiety being *syn* to the carbo alkoxy group in **6a–d** and **7a–d**. NOE are also consistent with endo addition to the lactam for **6a–c** and **7a–c**. It is also noteworthy that for **6a** and **6d** NOE and $^3J_{HH}$ suggest a conformationally rigid orientation for the silylmethylene in which the triisopropylsilyl moiety points away from the ring system.

In summary, the Lewis acid mediated addition of triisopropylallylsilane to chiral unsaturated bicyclic systems **5**[8] has been shown to furnish cyclobutane (**6**) or cyclopentane (**7**) derivatives in moderate to good yields. By appropriate choice of reaction temperature, either of these products can be almost exclusively obtained. In addition, the cyclobutane adducts may be the first confirmed examples of a Lewis acid mediated [2 + 2] addition of an allylsilane to an electron deficient alkene.[1b,3]

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Supplementary Material Available: General experimental procedures and characterization data (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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[8] All starting materials (**5a–d**) were prepared according to procedures described in: (a) Meyers, A. I.; Lefker, B. A.; Sowin, T. J.; Westrum, L. J. *J. Org. Chem.* **1989**, *54*, 4243. (b) Romo, D. Ph.D. Dissertation, Colorado State University, 1991. (c) Westrum, L. J. Ph.D. Dissertation, Colorado State University, 1993. (d) Meyers, A. I.; Snyder, L. *J. Org. Chem.* **1992**, *57*, 3814. Lactams **5a**, **5b**, and **5d** are new derivatives and are described in the supplementary material.

[9] The author has deposited atomic coordinates for **6d** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.