We have demonstrated in this report that (1) α-silylated vinyl ketones successfully trap even readily equilibrated lithium enolates under aprotic conditions; (2) the presence of copper is not required to account for the observed results, the "copper" enolate being indistinguishable in this case from the lithium enolate; and (3) an efficient synthesis of steroids is possible utilizing the reductive annelation procedure. This procedure seems to be amenable to large scale application bound by the costs of the silicon reagents, and the need to shrink ring D to obtain steroids of the natural series.

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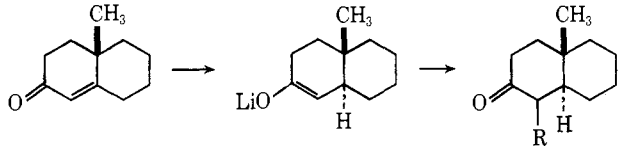
Regiospecific Michael Reactions in Aprotic Solvents with α-Silylated Electrophilic Olefins. Application to Annelation Reactions

Sir:

The discovery that lithium enolates of asymmetric ketones can be generated regiospecifically[1,2] coupled with the original demonstration that such *lithium* enolates could be alkylated and carboxylated (*cf.* **1** → **2**, **3**)

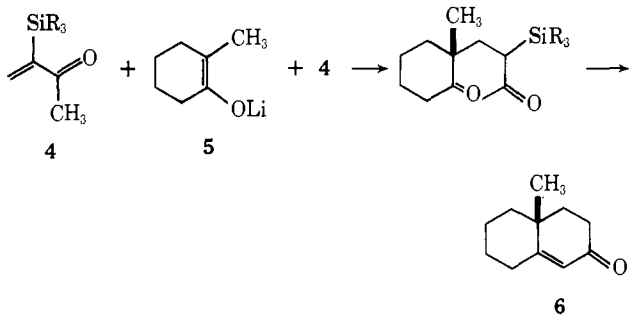


1 **2**, R = CH_3 **3**, R = CO_2H

more rapidly than they undergo equilibration *via* proton transfers[1] greatly extended the synthetic possibilities for the construction of complex structures.

Our original work was confined (if one excepts the carboxylation reactions) to the use of reactive alkyl halides[3] and it became increasingly evident that important progress would result if regiospecifically generated lithium enolates could be used in two of the other fundamental processes for forming carbon–carbon bonds, the aldol and the Michael reactions. We deal elsewhere with the regiospecific aldol condensation[4] and wish to report here on the regiospecific Michael reaction with lithium enolates.

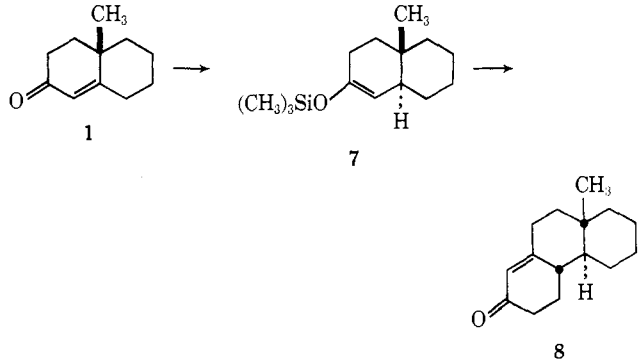
We have recently taken the first step in the solution of this problem with the demonstration that α-trialkylsilyl vinyl ketones such as **4** can be condensed with some regiospecifically generated lithium enolates in aprotic solvents (*e.g.*, **5** → **6**)[5]



4 **5** **6**

We initially considered, as did Boeckman,[6] that the enolate equilibration we had encountered, might be suppressed by making the enolate metal bond less easily dissociated. We were indeed successful with diethyl aluminum enolates (from addition of one equivalent of diethylaluminum chloride to the lithium enolate) but eventually realized that with careful attention to details[7] the original procedure[5] is in fact applicable and leads in high yield to regiospecific Michael reactions. Because of the importance of the reaction we report it here in detail.

The most general procedure involves trapping of a regiospecifically generated enolate (*e.g.*, from lithium–ammonia reduction in the presence of 0.8 equiv of *tert*-butyl alcohol) with trimethylchlorosilane, and regenerating the lithium enolate from the isolated enol silyl ether.[8] This procedure has the advantage that the silyl ether can be examined spectrally, to establish its structural homogeneity, before proceeding with the Michael reaction. We illustrate this for the annelation of **1** to **8**.[9]



1 **7** **8**

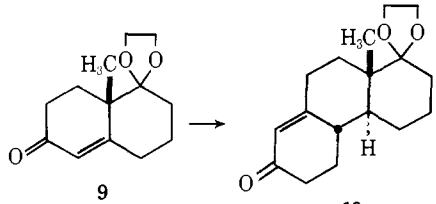
To a solution of 3 g-atoms lithium in dry, distilled liquid ammonia was added dropwise a solution of 1 equiv of enone **1** in tetrahydrofuran (4 ml/mmol) containing 0.8 equiv of *tert*-butyl alcohol. Excess lithium was destroyed after 5 more minutes with isoprene. Removal of the ammonia, finally under oil pump vacuum at ~40° for *ca.* 10 min, gave a residual white

(1) G. Stork, P. Rosen, and N. L. Goldman, *J. Amer. Chem, Soc.*, **83**, 2965 (1961).
(2) G. Stork, P. Rosen, N. L. Goldman, R. V. Coombs, and J. Tsuji, *J. Amer. Chem. Soc.*, **87**, 275 (1965).
(3) For applications to reactive, functionally substituted halides, *cf.*, *inter alia*, G. Stork, S. Danishefsky, and M. Ohashi, *J. Amer. Chem. Soc.*, **89**, 5459 (1967); G. Stork, S. Uyeo, T. Wakamatsu, P. Grieco, and J. Labovitz, *J. Amer. Chem. Soc.*, **93**, 4945 (1971); G. Stork and M. Jung, *J. Amer. Chem. Soc.*, **96**, 3682 (1974).
(4) (a) G. Stork and J. D'Angelo, in preparation; (b) G. Stork and G. Kraus, in preparation.
(5) G. Stork and B. Ganem, *J. Amer. Chem. Soc.*, **95**, 6152 (1973).
(6) We now believe that earlier difficulties were due to the adventitious presence of traces of protic impurities in the medium. The glyme used in the present experiments was distilled from fresh lithium aluminum hydride and great care was used to prevent access of moisture to the system at all times.
(7) Professor R. K. Boekman, Jr. (*J. Amer. Chem. Soc.*, **96**, 6179 (1974)) reports, his successful, independent, efforts to ensure regiospecificity in annelation with the silyl vinyl ketone reagents. We thank him for communicating his results to us in advance of publication.
(8) G. Stork and P. F. Hudrlik, *J. Amer. Chem. Soc.*, **90**, 4462, 4464 (1968).
(9) All operations were conducted under nitrogen. Base-catalyzed cyclizations were carried out in deoxygenated media.

solid[10] which was dissolved in tetrahydrofuran at room temperature, cooled to −10°, and treated with ~50% excess of 1:1 chlorotrimethylsilane–triethylamine.[11] Addition of pentane after stirring for 10 min, followed by addition of, and washing with, ice-cold saturated aqueous sodium bicarbonate, washing with brine, and drying gave the silyl enol ether **7** in 90% yield after distillation (Kugelrohr, 65° (0.7 mm)). The nmr spectrum showed a 3 H methyl singlet at δ($CDCl_3$) 0.9 ppm and a 1 H doublet ($J \sim 1$ Hz) at 4.5 ppm.

Dropwise addition of the silyl ether **7** in *dry* glyme (4 ml/mmol) to 1.05 equiv of ethereal methyl lithium in glyme (4 ml/mmol) was followed by stirring at room temperature for 30 min, cooling to −78° under a stream of nitrogen, adding 1.2 equiv of the unsaturated ketone **4**, R = CH_3,[12] in glyme, stirring for 10 min, and allowing to warm over 30 min. Work-up (saturated ammonium chloride solution), followed by refluxing with 5% sodium methoxide in methanol for 3 hr, gave (67% yield) the known tricyclic enone **8**, mp 122°, identical with an authentic sample.[2]

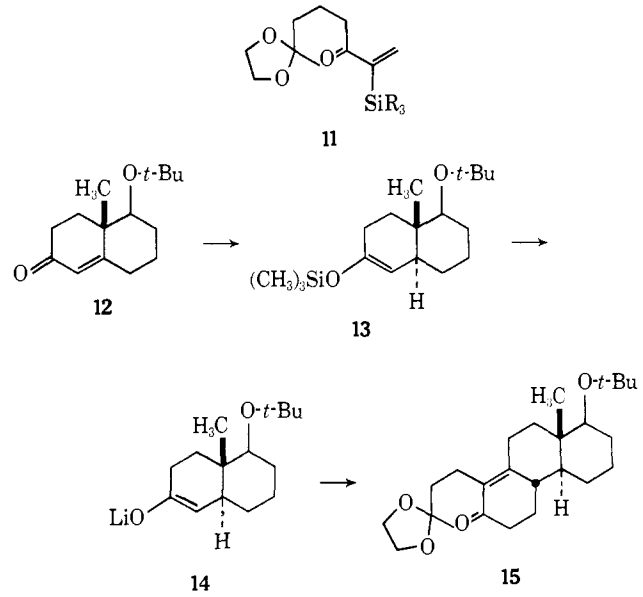
Under the same conditions, the octalone **9**[13] was transformed, *via* the trimethylsilyl enol ether (nmr: δ ($CDCl_3$) 0.94 (3 H, s), 4.7 (1 H, b s) from reductive trapping, into the tricyclic ketone **10**, mp 141–142°:



9 10

nmr δ 1.1 (3 H, s), 3.9 (4 H, s), 5.8 (1 H, b s). Acid hydrolysis converted **10** into the known corresponding dione, mp 122°.[14]

The use of the bis-annelating reagent **11** allows, as we have previously shown,[5] the addition of the equivalent of two rings at a time, thus leading to the type of tricyclic enone which we previously used[15] in the synthesis of (±)-progesterone. Under the conditions described for the conversion of **1** to **8**, the silyl ether **13** (88% yield after Kugelrohr distillation at 75° (0.01 mm)) from the reductive trapping of **12**[16] was reconverted to the lithium enolate **14** which was treated with **11**, R = CH_3, and cyclized to give **15** (74% yield) mp 122°, identical with an authentic sample.[17]



11 12 13 14 15

The stereo- and regiospecific transformation, *via* reductive methylation, of tricyclic enones, such as **15**, to natural steroids has been described previously.[15]

It is clear that the growing usefulness of regiospecifically generated lithium enolates can now be extended to the Michael reaction, even with electrophilic olefins possessing exchangeable hydrogens.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health for their support of this investigation.

(10) This mixture of lithium enolate and lithium *tert*-butoxide formed in the lithium ammonia reduction (*e.g.*, of **1**) can be used directly, without prior conversion to the silyl ether **7**, simply by adding the α-silylvinyl ketone to the dry lithium salts dissolved in glyme, under the conditions described below for the lithium salt derived from **7**. The tricyclic ketone **8** is thus obtained, although in somewhat lower yield.

(11) Previously centrifuged to remove some triethylamine hydrochloride.

(12) The trimethylsilyl vinyl ketones used here are somewhat more conveniently prepared from (commercially available) trimethylvinylsilane, exactly as described previously for the triethyl analogs (see ref 7). We established that the use of the triethylsilyl vinyl ketone **4**, R = C_2H_5, is also successful in the transformation of **1** into **8**. No evidence for the linear tricyclic isomer which would result from prior equilibration of the enolate was found in this case or in the others reported here.

(13) E. J. Corey, M. Ohno, R. B. Mitra, and P. A. Vatakencherry, *J. Amer. Chem. Soc.*, **86**, 478 (1964).

(14) G. Stork, *Pure Appl. Chem.*, **9**, 131 (1964). This was characterized by its (correct) high resolution mass spectrum, as was **10**.

(15) G. Stork and J. E. McMurry, *J. Amer. Chem. Soc.*, **89**, 5464 (1967). The present annelation method represents a much simpler method than any previously devised and the overall yield is also definitely better.

(16) Z. G. Hajos, R. A. Micheli, D. R. Parrish, and E. P. Oliveto, *J. Org. Chem.*, **32**, 3008 (1967).

(17) Prepared by a different route (ref 4a). Identity was established by conversion to (±)-D-homo-19-nortestosterone which was compared with an authentic sample (ref 15).

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Conformational Analysis of Hydrocarbon Chains in Solution. Carbon Tetrachloride

Sir:

Very little is known about the conformational preferences of hydrocarbon chains longer than heptane and shorter than polyethylene, either in the gas phase[1] or in solution.[2] We present evidence which demonstrates the flexible nature and random orientation of hydrocarbon chains in carbon tetrachloride solution.

Our probe of chain conformation is a benzophenone substituted with a remotely attached hydrocarbon chain.[3] Conformations of the chain in which the chain

(1) (a) J. C. McCoubrey, J. N. McCrae, and A. R. Ubbelohde, *J. Chem. Soc.*, 1961 (1951); (b) R. S. Stein, *J. Chem. Phys.*, 21, 1193 (1953); (c) L. S. Bartell and D. A. Kohl, *J. Chem. Phys.*, **39**, 3097 (1963); (d) R. A. Bonham, L. S. Bartell, and D. A. Kohl, *J. Amer. Chem. Soc.*, **81**, 4765 (1959); (e) K. S. Pitzer, *Ind. Eng. Chem.*, **36**, 829 (1944); *J. Chem. Phys.*, **8**, 711 (1940); (f) E. F. Meyer and K. S. Stec. *J. Amer. Chem. Soc.*, **93**, 5451 (1971).

(2) (a) G. W. Brady, C. Cohen-Addad, and E. F. X. Lyden, *J. Chem. Phys.*, **51**, 4039 (1969;) (b) G. W. Brady, *Accounts Chem. Res.*, 7, 174 (1974); (c) K. Liu and R. Ullman, *J. Polym. Sci., Part A-2*, **6**, 451 (1968); (d) K. Liu, *ibid.*, **5**, 1209 (1967).