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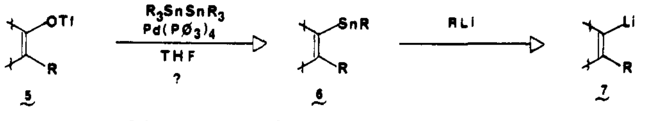
A Regioselective Entry to Vinyllithiums from Unsymmetrical Ketones via Enol Triflates†

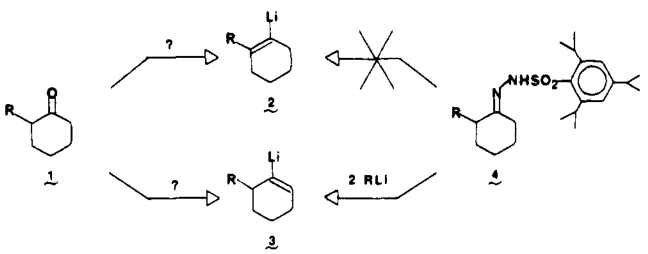
Summary: The first method for the regioselective preparation of either the "kinetic" or "thermodynamic" vinyllithium from an unsymmetrical ketone is described.

Sir: The importance of organolithium compounds to the synthetic chemist can hardly be overestimated. Real utility has necessarily been contingent upon the development of facile and selective methods for the preparation of organolithium compounds. One device that can now be routinely employed to control the regioselectivity of aryl- and vinyllithium formation is the use of heteroatoms for directing metalations.[2] One of the more important methods for the regioselective preparation of vinyllithiums is from ketones via their hydrazones.[3,4] The trisylhydrazone 4, derived from an unsymmetrical ketone can be fragmented to the less substituted vinyllithium 3 according to Bond's modification[3] of the Shapiro reaction;[5] however, the more highly substituted vinyllithium 2 is not accessible from hydrazones (Scheme I). We describe herein the first general method for regioselective entry to both the "kinetic" and "thermodynamic" vinyllithiums from unsymmetrical ketones.

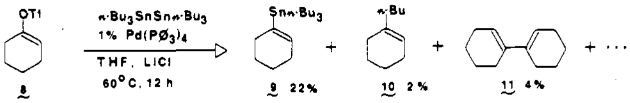
It has been well established that vinylstannanes will undergo transmetalations with alkyl- or aryllithiums to generate vinyllithiums.[6,7] Alternatively, vinylstannanes can be converted to vinyllithiums via their corresponding halides. A new and general route to vinylstannanes is suggested by the recent and rather significant observations of Scott, Crisp, and Stille.[8] They observed that tetrakis(triphenylphosphine)palladium can catalyze the coupling of vinyl triflates with a variety of organostannanes (vinyl, alkynyl, alkyl). Extension of this chemistry to the current problem raises the question of whether the coupling of a vinyl triflate and a distannane can be effected to give vinylstannanes. A few examples have been recently reported concerning related coupling of vinyl triflates with stannylaluminiums and stannylmagnesiums, but these reactions do not appear to be synthetically useful.[9]



Scheme I



The palladium-catalyzed coupling of 1-cyclohexenyl triflate with hexabutyldistannane produced the desired vinylstannane 9 in a disappointingly low yield. This result would be understandable if, as is possible,[8] the product vinylstannane 9 were to compete with hexabutyldistannane in the coupling reaction with the vinyl triflate. However, only a small amount of 1,1′-bicyclohexenyl could be found. The only other low molecular weight compound ($M_r < 500$) that could be found was 1-*n*-butylcyclohexene (2%).



The coupling reactions of a variety of enol triflates were found to be highly successful with hexamethyldistannane, perhaps due to its more sterically accessible tin-tin bond.[10] Most of the vinyltrimethylstannanes indicated in Table I could be easily isolated from reaction mixtures that were exceptionally clean as indicated by capillary GC. The following procedure for the preparation of 6-methyl-1-trimethylstannylcyclohexene **25** is typical. A 50-mL round-bottom flask was charged in order with 5.0 mL of THF, 0.191 g (0.78 mmol) of the enol triflate 8, 0.230 g (0.702 mmol) of hexamethyldistannane, 0.21 g (4.95 mmol) of lithium chloride, and 0.012 g (0.014 mmol) of tetrakis(triphenylphosphine)palladium(0). The mixture was deoxygenated by the freeze-thaw method (−196 → 25 °C, three cycles) and stirred at 60 °C for 10 h under argon. The initially yellow mixture became colorless and usually became dark at the end of the reaction. Upon verifying by GC that all of the distannane was consumed, the reaction mixture was partitioned between a pH 7 buffer and

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[10] The corresponding coupling reaction with hexamethyldisilane failed. The reaction of 8 with (trimethylstannyl)trimethylsilane gave a 19% yield of 1-cyclohexenyltrimethylsilane along with a 12% yield of 12.

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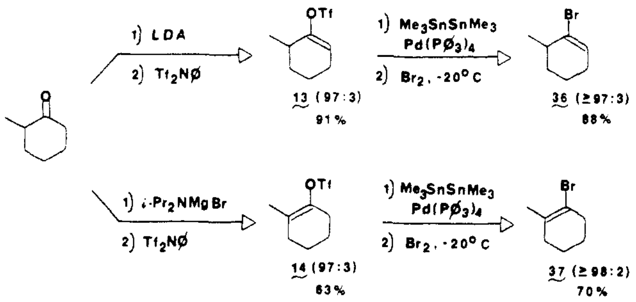
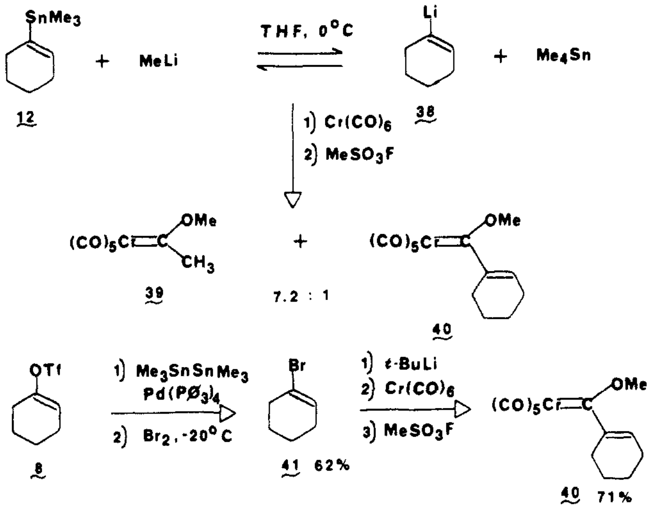
Scheme II



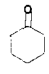
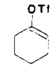
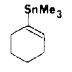
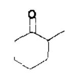
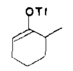
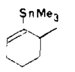
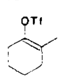
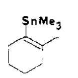
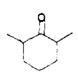
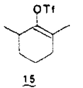
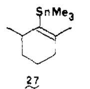
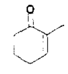
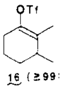
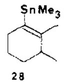
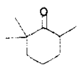
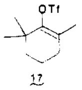
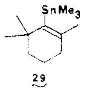
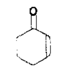
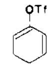
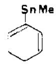
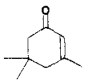
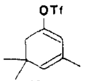
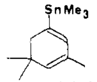
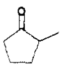
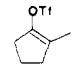
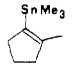
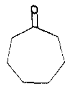
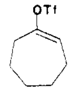
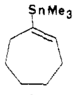
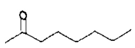
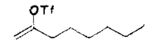
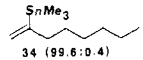
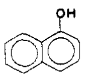
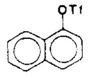
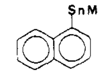
Scheme III



ether. After filtration, drying, and concentration of the organic layer, the product was chromatographically isolated from the crude mixture by elution through silica gel with hexanes to give 0.152 g (84%) of **25**.[11] The use of a stoichiometric deficiency of hexamethyldistannane precludes a separation problem during silica gel chromatography. As indicated in Table I some of the more highly substituted vinylstannanes such as **26** are difficult to isolate due to protonolysis and can be isolated chromatographically only if the silica gel is pretreated with triethylamine and/or the eluent (hexanes) contains 1% triethylamine.

The preparation of both possible isomeric vinylstannanes from unsymmetrical ketones is limited only by the ability to selectively prepare the "kinetic" and "thermodynamic" ketone enolates. The isomeric methyl-substituted (trimethylstannyl)cyclohexenes **25** and **26** can both be obtained from 2-methylcyclohexanone since methods have been developed for the selective preparation of either of the enol triflates **13**[12] or **14**[13] in 97% isomeric purity from the reaction of the corresponding lithium enolates with *N*-phenyltrifluoromethanesulfonimide.[14] The isomeric purity of the vinylstannanes **25** and **26** could not be determined since they had the same retention time on capillary GC. As indicated in Scheme II, these triflates can be converted to the corresponding bromides **36** and **37** by quenching the coupling reaction mixture with bromine. Analysis of the bromides reveals that the isomeric purity is retained in the coupling reaction. The vinyl

Table I. Palladium-Catalyzed Coupling of Enol Triflates and Hexamethyldistannane[a]

ketone	enol triflate (regioselectivity)	yield (method)	vinyl stannane	reaction time[1]	yield[2] isolated (GC)
	 8	84% (A)[3]	 12	3 h	81%[4] (88%)
	 13 (97:3)	91 (A)[3]	 25	9	84
	 14 (97:3)	63 (B)[5] 90[6a]	 26	168[6b]	80[7]
	 15	69 (A)[3]	 27	120[8]	62[7] (60)
	 16 (≥99:1)	72 (C)[9]	 28	120[8]	67[7] (72)
	 17	82 (A)[3]	 29	240[10]	39[7] (37)
	 18 (≥99:1)	70 (A)[3]	 30	4[11]	72
	 19	54 (D)[12]	 31 (92:4:4)	4	80[7,13]
	 20 (99.7:0.3)	63 (E)[14] 15 (B)[5]	 32	96[8]	80[7] (96)
	 21	89 (A)[3]	 33	0.75	73
	 22 (94:6)	70 (A)[3]	 34 (99.6:0.4)	6	74[15]
	 23	65 (F)[16]	 35	168	86

[a] (1) Unless otherwise specified the coupling reactions were carried out at 60 °C with 0.2 M THF solutions of the enol triflate with 0.9 equiv of hexamethyldistannane, 6.0 equiv of lithium chloride, and 0.018 equiv of tetrakis(triphenylphosphine)palladium(0) under an argon atmosphere. (2) All isolated yields were of material obtained after column chromatography on silica gel with hexanes; all GC yields were determined with an FID on a 25 m × 0.32 mm OV-1701 column with camphor as internal standard. (3) Method A: LDA, *N*-phenyltrifluoromethanesulfonimide (ref 8). (4) Tetrakis(triphenylphosphine)platinum under the same conditions gave a 53% yield (GC) after 336 h. (5) Method B: *i*-Pr$_2$NMgBr, *N*-phenyltrifluoromethanesulfonimide. (6) [a] reference 13d; [b] 5 mol % of catalyst added in two portions. (7) Coupling reaction carried out in the presence of 1 equiv of anhydrous lithium carbonate and the vinylstannane was isolated on silica gel that had been pretreated with triethylamine upon elution with hexanes that contained 1% triethylamine (1% dimethylethylamine in pentane for **32**). (8) 5 mol % of the palladium(0) catalyst. (9) Method C: Me$_2$CuLi·Me$_2$S, *N*-phenyltrifluoromethanesulfonimide (ref 12). (10) 8 mol % catalyst added in four portions. (11) 0.45 mol % catalyst. (12) Fe(0)/MeMgBr, Me$_3$SiCl; MeLi, *N*-phenyltrifluoromethanesulfonimide (ref 18). (13) Reference 18 reports a 2:96:2 ratio of silyl enol ethers from isophorone; the vinyl stannane **31** was obtained as a 4:92:4 mixture of isomers. (14) Method E (from 2-methylcyclopentenone): L-Selectride, *N*-phenyltrifluoromethanesulfonimide (ref 13d). (15) After separation from 2,2′-bi-1-octenyl, **34** is obtained in 74% yield as 99.6% isomerically pure material. (16) Method F: *n*-BuLi, trifluoromethane sulfonic anhydride.

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[11] Unless otherwise stated satisfactory spectral data and elemental analysis or high-resolution mass spectra were obtained for all new compounds.

[12] McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, 979.

[13] (a) Crisp, G. T.; Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 7500. (b) Krafft, M. E.; Holton, R. A. *Tetrahedron Lett.* **1983**, 1345. (c) Scott, W. J.; Pena, M. R.; Swärd, K.; Stoessel, S. J.; Stille, J. K. *J. Org. Chem.* **1985**, *50*, 2302. (d) Crisp, G. T.; Scott, W. J. *Synthesis* **1985**, 335.

[14] *N*-phenyltrifluoromethanesulfonimide was purchased from SCM Chemicals (catalog no. 11978-4) but now is also available from Aldrich Chemical Co. (catalog no. 29597-3).

bromides **36** and **37** are apparently unknown; however, procedures for the preparation of the corresponding iodides and chlorides have been reported that give isomeric mixtures.[15,16] A very recent report describes the first method where either of the chlorides corresponding to **36** or **37** can be made to predominate.[17] The selective preparation of the vinylstannane **28** is made possible by the trapping of the enolate generated by the conjugate addition of lithium dimethylcuprate to 2-methylcyclohexenone.[12] The 2-(trimethylstannyl)-1,3-cyclohexadiene **24** is accessible from the kinetic enolate of cyclohexenone, whereas, the preparation of the 1-(trimethylstannyl)-1,3-cyclohexadiene **31** is made possible by a procedure recently introduced by Krafft and Holton for the preparation of the thermodynamic enol derivatives of cyclohexenones.[18] The need for excess catalyst over the standard amount in some of the reactions in Table I can be obviated by addition of 5 mol % triphenylphosphine.

The cleavage of vinylstannanes with alkyllithiums is an often used method for the convenient generation of vinyllithiums.[6,7] Caution should be exercised in the synthetic applications of these transmetalations since they are equilibrium reactions[6] which may not be favorable in all cases nor may all electrophiles have favorable rate constants for reaction with the predominate species. For example, in an effort to prepare the cyclohexenyl chromium carbene complex **40**, a THF solution of the vinylstannane **12** that had been pretreated with 1 equiv of methyllithium was transferred to a solution of chromium hexacarbonyl. Upon methylation a 7.2/1.0 mixture of the methyl carbene complex **39** and the cyclohexenyl complex **40** was obtained (Scheme III). The same result was obtained by starting with cyclohexenyllithium and tetramethylstannane.[19] Thus, at least with chromium carbonyl as the electrophile, it is necessary to generate the vinyllithium from the corresponding halide which can be readily obtained from the triflate by quenching the coupling reaction with a halogen.

The palladium(0)-catalyzed coupling of enol triflates and hexamethyldistannane provides for a new synthesis of vinylstannanes and thus a new synthetic entry to vinyllithiums. The vinylstannanes can be regioselectively prepared from unsymmetrical ketones in two steps wherever the metal enolates of the ketones can be generated selectively.

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Supplementary Material Available: Experimental procedure for **26** and spectral data for compounds **10–23**, **25–34**, **36**, and **37** (7 pages). Ordering information is given on any current masthead page.

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[15] Chlorides: (a) Montgomery, L. K.; Applegate, L. E. *J. Am. Chem. Soc.* **1967**, *89*, 2952. (b) Mousseron, M.; Jacquier, R. *Bull. Soc. Chim. Fr.* **1950**, 648. Iodides: Bottini, A. T.; Corson, F. P.; Fritzgerald, K.; Frost, K. A., II. *Tetrahedron* **1972**, *28*, 4883.

[16] A selective preparation of 2-methyl-1-chlorocyclohexene has been described: Gassman, P. G.; Valcho, J. J.; Proehl, G. S.; Cooper, C. F. *J. Am. Chem. Soc.* **1980**, *102*, 6519.

[17] Hudrlik, P. F.; Kulkarni, A. K. *Tetrahedron* **1985**, *41*, 1179.

[18] Krafft, M. E.; Holton, R. A. *J. Am. Chem. Soc.* **1984**, *106*, 7619.

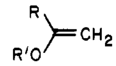
[19] The combined yield of **38** and **39** is 17% from both sides of the equilibrium. The reason for the low overall yield is not understood.

Stereoselection in the Michael Addition Reaction. 4. Diastereofacial Preferences in Lewis Acid Mediated Additions of Enolsilanes to Chiral Enones[1]

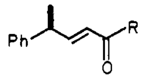
Summary: Chiral enones show good to excellent diastereofacial preference in their $TiCl_4$-mediated reactions with achiral and chiral enolsilanes; the method is shown to be useful for the preparation of acyclic 1,5-diketones and 1,5-keto acids having two or three stereocenters.

Sir: In a previous publication in this series,[2] we have reported that chiral aldehydes show high intrinsic diastereofacial preferences in their Lewis acid mediated reactions with enolsilanes and ketene acetals. Interestingly, these aldehydes show only modest diastereofacial preferences in their reactions with allylsilanes.[3] We have now extended our study to the reactions of the Lewis acid mediated reactions of chiral enones with enolsilanes and ketene acetals and report herein that good to excellent diastereofacial preferences are observed.

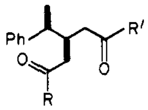
For our initial study, which addressed the question of diastereofacial preference of the enone only, the achiral enolsilanes **1–4** and chiral enones **5–7** were employed. Reactions were carried out by premixing the enone and titanium tetrachloride in methylene chloride at −78 °C. Excess enolsilane (1.3–2.9 equiv) was added over a period of 30 min, and the reaction was quenched after 1 h by the addition of aqueous potassium carbonate. Diastereomer ratios were obtained by capillary GLPC or proton NMR spectroscopy on the crude product mixture. In each case, the products were mixtures of two diastereomers (**8**/**9**, **10**/**11**, **12**/**13**, or **14**/**15**). Stereostructures were determined by ^1H NMR spectroscopy, using the relative chemical shifts of the R and R′ resonances, as has been discussed previously.[3,4] Results are shown in Table I.



1: R = *t*-Bu, R′ = Me_3Si
2: R = *t*-Bu, R′ = *t*-$BuMe_2Si$
3: R = Ph, R′ = Me_3Si
4: R = *t*-BuO, R′ = *t*-$BuMe_2Si$



5: R = Me
6: R = *t*-Bu
7: R = Ph



8: R = Me, R′ = *t*-Bu
9: R = *t*-Bu, R′ = Me
10: R = Me, R′ = Ph
11: R = Ph, R′ = Me
12: R = *t*-Bu, R′ = Ph
13: R = Ph, R′ = *t*-Bu
14: R = OH, R′ = *t*-Bu
15: R = *t*-Bu, R′ = OH

As shown in the table, diastereomer ratios are uniformly good, falling in the range from 8:1 to >30:1. In all cases the major isomer results from *ul* topicity (attack of enolsilane on the *re* face of the *S* enantiomer of the enone).[5,6]

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[1] Part 34 in the series "Acyclic Stereoselection". For part 33, see: Heathcock, C. H.; Finkelstein, B. E.; Aoki, T.; Poulter, C. D. *Science (Washington, D.C., 1883–)* **1985**, *229*, 862.

[2] Heathcock, C. H.; Flippin, L. A. *J. Am. Chem. Soc.*, **1983**, *105*, 1667.

[3] Heathcock, C. H.; Kikooka, S.-T.; Blumenkopf, T. A. *J. Org. Chem.* **1984**, *49*, 4214.

[4] Heathcock, C. H.; Lampe, J. *J. Org. Chem.* **1983**, *48*, 4330.