## USE FUL SYNTHETIC REAGENTS DERIVED FROM 1-TRIISOPROPYLSILYLPROPYNE AND 1, 3-<u>BIS</u>-[TRIISOPROPYLSILYL]PROPYNE. DIRECT, STEREOSELECTIVE SYNTHESIS OF EITHER Z OR E ENYNES

E. J. Corey and Christoph Rucker

Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138 USA

<u>Summary</u>. Lithic reagents derived from 1-trinsopropylsilylpropyne (1) and 1, 3-<u>bis</u>-[trinsopropylsilyl]propyne (3) are effective for the synthesis of <u>Z</u> or <u>E</u> terminal environments (CH=CH-C=CH) and for carbon-carbon bond formation with halides, aldehydes, ketones, epoxides, and  $\alpha,\beta$ -enones.

We recently described a simple synthesis of trusopropylsilyltriflate (TIPS-Trf), an excellent reagent for the introduction of the TIPS group at nucleophilic centers.<sup>1</sup> It was also pointed out that the TIPS group has excellent potential as a control element in synthesis since the three isopropyl groups provide strong steric screening not only for the silicon to which they are attached but to the next atom and even beyond.<sup>1</sup> For example, in a phenolic TIPS ether the carbons ortho to oxygen are sterically shielded. In addition, it is clear that because of the bulk of the TIPS group, a greater measure of stereochemical control and position selectivity in carbon-carbon bond forming processes might result from the use of this group rather than the more common trimethylsilyl unit. In this note we illustrate the uniqueness and utility of TIPScontaining reagents for the case of two prototypical propargylic nucleophiles.

1-TIPS-propyne (1), bp 100-101° (5mm), was readily prepared in 87% yield from 1-lithiopropyne and 1 equiv of TIPS-Trf in ether at -40° to 0°. It undergoes clean metallation with either <u>n</u>-butyllithium-tetramethylenediamine in ether (-15°, 2 hr), or <u>t</u>-butyllithium in ether-pentane (-10°, 4 hr) or <u>n</u>-butyllithium in tetrahydrofuran (THF) (-20°, 15 min) to form lithio 1-TIPSpropyne (2) which can be converted to 1, 3-<u>bis</u>-TIPS-propyne (3), bp 130-135° (0.08 mm), 100% yield, by reaction with a slight excess of TIPS-Trf (-78 to -40°, 1 hr).<sup>2</sup>

TIPS-C=C-CH<sub>3</sub> (TIPS-C=C-CH<sub>2</sub>) Li TIPS-C=C-CH<sub>2</sub>-TIPS  
1 
$$\frac{2}{3}$$

Reaction of  $\frac{3}{2}$  with 1 equiv of <u>n</u>-butyllithium in THF at -20° for 15 mm results in deprotonation to form lithiated  $\frac{3}{2}$  which is a highly useful reagent for the synthesis of either <u>cis</u> or <u>trans</u> enynes, a subject previously studied in these laboratories in connection with the synthesis of histrionicotoxin.<sup>3,4</sup>

Addition of cyclohexane carboxaldehyde to the lithio derivative of  $\frac{3}{2}$  m THF at -78° followed by gradual warming (ca. 6 hr) to 23°, extractive isolation and filtration through silica gel afforded cis enyne 4, R = cyclohexyl, with >20 1  $\underline{Z}/\underline{E}$  stereoselectivity (pmr analysis), m 71% yield. Similarly <u>n</u>-heptanal and trimethylacetaldehyde afforded 4,  $R = \underline{n} - C_6 H_{13}$ , (57%) and 4,  $R = \underline{t} - Bu$ , (79%) with comparable stereoselectivity.



In contrast, when the same reactions were conducted in THF with 5 equiv of hexamethylphosphorictriamide (HMPA) (relative to aldehyde) at -78° for 15-20 seconds (followed by quenching at -78° and isolation) the <u>trans</u> enynes 5,  $R \approx$  cyclohexyl, <u>n</u>-C<sub>6</sub>H<sub>13</sub> and <u>t</u>-Bu, were formed with <u>E/Z</u> ratios in the range 20:1 to 10:1 and yields of 60-65%. The lithio derivative of 1-TIPS-3-TMS-propyne in contrast afforded no enyne product at all under these conditions.

Thus, with the aldehydes <u>n</u>-heptanal, cyclohexane carboxaldehyde, and trimethylacetaldehyde, in which the formyl function is situated either on a 1°, 2°, or 3° carbon, a simple method is now available for the synthesis of enynes 4 or 5 with high selectivity and in good yield. Aromatic aldehydes seem to deviate from this pattern, however. Benzaldehyde, for example, affords 4 and 5,  $R = C_6H_5$ , in a ratio of 2·1 in THF and 1:9 in THF containing 1 equiv of HMPA. For <u>p</u>-anisal dehyde the ratios of 4 to 5 were 6:1 in THF and 1.4.5 for THF containing 1 equiv of HMPA. Thus, there is an interesting and substantial effect of the <u>p</u>-methoxy substituent to increase stereoselectivity for formation of <u>Z</u> enyne in THF, that is to displace the behavior of this substrate toward that of non-aromatic aldehydes.

We rationalize these results as follows. In THF solution the lithiated 3 probably exists at least partially as the lithic allene 6. Reaction of 6 with the aldehyde through a 6-membered cyclic transition state with minimal steric repulsion is expected to lead to 4. In THF-HMPA



solution the anionic conjugate base of  $\frac{3}{2}$  may be a major species and probably is the most active nucleophile. Reaction of this allenic/propargylic anion via minimum repulsion transition state 7 would afford the observed <u>E</u> enyne 5.





The lack of high stereoselectivity with benzaldehyde as substrate could be a result of its greater electron affinity (i.e., stability of the radical anion  $C_6H_5CHO^{\bullet}$ ) and the intervention of a competing electron transfer pathway.<sup>5,6</sup> The occurrence of substantially greater <u>Z</u> stereoselectivity with p-anisaldehyde in THF relative to benzaldehyde supports this view.

That the effect of HMPA in favoring formation of E -enyne 5 over Z -enyne 4 is due to the carbonyl addition step and not to a special influence on the mode of further reaction of the aldehyde carbonyl adduct could be demonstrated in a straightforward way. Reaction of cyclohexanecarboxal dehyde with lithio 3 in THF at -78° for 10 sec, quenching with pH 7 buffer at -78°, extractive isolation and chromatography gave the erythro  $\beta$ -hydroxysilane 8 in 12% yield along with the two allenic isomers (11% total), starting aldehyde and Z-enyne 4, R = cyclohexyl. The erythro stereochemistry of the adduct 8 was supported by (1) the pmr spectrum which showed  $J_{AB} = 1$  5 Hz, (2) conversion with <u>n</u>-butyllithium in THF exclusively to <u>Z</u>-enyne 4, R = cyclohexyl; and (3) conversion by trifluoroacetic acid or boron trifluoride to  $\underline{\mathbf{E}}$ -enyne 5, R = cyclohexyl. Treatment of 8 in THF-HMPA at  $-78^{\circ}$  with <u>n</u>-butyllithium afforded again the Z-enyne as major product (ratio  $\underline{Z}/\underline{E}$  ca. 6). Thus it is evident that HMPA does not reverse the stereochemistry of the elimination step and that its influence to favor E-enyne formation from lithio 3 is exerted at the prior stage of reaction, <u>i</u> e., carbonyl addition to cyclohexane carboxyldehyde. (It should be noted that 4 and 5 are stable under the reaction conditions in THF or THF-HMPA.)

Subsequent to our discovery of the use of lithic  $\frac{3}{2}$  for the conversion of aldehydes to either  $\underline{Z}$ - or  $\underline{E}$ -enynes as described above, a communication from the laboratory of Prof. H. Yamamoto (Nagoya University) appeared in which the use of magnesic derivatives of various silylated propynes other than  $\frac{3}{2}$  in THF for the preparation of  $\underline{Z}$ -enynes is described. <sup>7</sup> Our results and those of Prof. Yamamoto are mutually consistent and consonant with the rationale presented above

We also report here on some uses of the reagent TIPSC  $\equiv$  CCH<sub>2</sub>L1 (2) as a more sophisticated version of Me<sub>3</sub>SiC $\equiv$  CCH<sub>2</sub>L1 (9) introduced by us in 1968.<sup>8,9</sup> As is the case with 9, 2 is an effective reagent for the conversions RBr  $\rightarrow$  RCH<sub>2</sub>C $\equiv$ CSiR'<sub>3</sub> and R<sub>2</sub>CO (ketone)  $\rightarrow$  R<sub>2</sub>C(OH)CH<sub>2</sub>C $\equiv$ CSiR'<sub>3</sub> Such transformations of 2 occur cleanly with substrates such as benzyl bromide (THF, -78° to 23°, 16 hr, 96%), geranyl bromide (THF, -78° to 23°, 16 hr, 78%), cyclohexanone (THF, -78° to 23°, 16 hr, 63%) with at most only traces of allenic by-product However, in contrast with 9 which reacts with aldehydes to afford both allenic and acetylenic adducts as major products, 2 reacts cleanly in ether -HMPA (2 1) at -78° to afford only acetylenic product according to the equation RCHO + 2  $\rightarrow$  RCH(OH)CH<sub>2</sub>C $\equiv$ CTIPS Smooth propargylation of oxiranes by 2 has also been observed as indicated by the following example:



Since the  $CH_2C\equiv CTIPS$  unit can be transformed readily into a wide variety of other substructures including among others  $CH_2COCH_3$ ,  $CH_2C\equiv CCOOCH_3$ ,  $CH_2C\equiv CCH_2OH$ ,  $CH_2CH_2COOH$ , <sup>10</sup> the versatility of 2 is clear.

Finally, we report that 2 in 3:1 THF-HMPA at -78° to -40° undergoes efficient conjugate addition to  $\beta$ -monosubstituted  $\alpha,\beta$ -enones, but 1, 2-addition in THF alone.



Earlier work on the  $\beta$ -propargylation of  $\alpha,\beta$ -enones had yielded only marginal results. Multistep sequences have also been used to effect this overall transformation.

## References and Notes

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