

1,2 and 1,4 Addition of Group IVA Anions to 2-Cyclohexenones.

Kinetic and Thermodynamic Product Control.

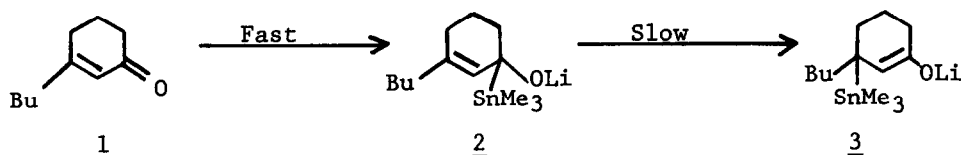
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For many years there has been a lively controversy on the mechanism of nucleophilic 1,2 and 1,4 additions to α,β -unsaturated carbonyl compounds. Various arguments based on reversibility, electron transfer, geometry and hard soft acid base (HSAB) theory have been advanced to explain experimental observations. In order to gain a better understanding of the additions of group IVA nucleophiles to enones, we have examined the kinetic and thermodynamic behavior of Me_3SnLi , Me_3SiLi and Me_3CLi with 2-cyclohexenones in various solvent systems. Our results correlate qualitatively with the relative stability of group IVA radicals and anions, the relative stability of 1,2 and 1,4 addition products, and are phenomenologically contrary to the predictions based on HSAB theory.

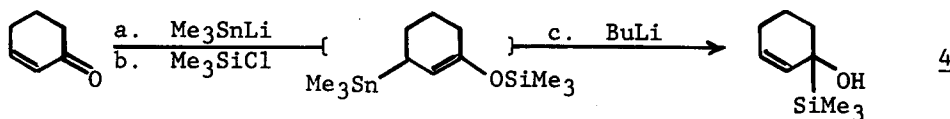
We recently reported¹ that trimethylstannyl lithium (Me_3SnLi) adds to 2-cyclohexenone in the 1,4 sense in tetrahydrofuran and in the 1,2 sense in diethyl ether. Since it was not clear at the time whether these results were due to mechanistically different kinetic processes or whether equilibration was involved, we have examined the reaction further. Experiments with 3-butyl-2-cyclohexenone (1) indicate that the 1,4 addition observed in THF is in fact the result of an extremely facile equilibration of 2 \rightleftharpoons 3. Thus when 1 was added to



Me_3SnLi in THF at -100°C and was quenched immediately with cold methanol, the 1,2 adduct 2 was found to be the major product.² Although the instability of 2 ($\text{Li} = \text{H}$) precluded VPC analysis, the proportions of the 1,2 and 1,4 addition products were readily determined by NMR integration of the trimethylstannyl resonances in benzene solution. These trimethyl singlets were displayed at 0.19

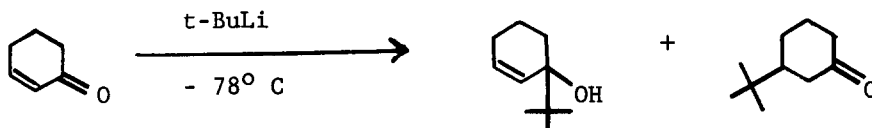
and 0.04 δ in the 1,2 and 1,4 adducts respectively. With diethyl ether the less basic nature of the solvent would be expected to favor a more tightly associated oxygen-lithium bond and thus slow equilibration to the more stable enolate 3. While rearrangement in ether was not detected in -78° C, warming an ethereal solution of 2 to room temperature resulted in conversion to 3 after 10 min. Thus the kinetic product of Me_3SnLi and 2-cyclohexenones appears to be largely if not completely the 1,2 adduct.

Trimethylsilyllithium (Me_3SiLi) reacts with 2-cyclohexenone in THF-HMPA to give exclusively the product of 1,4 addition.³ Although the product was postulated to the result of a kinetic 1,4 addition, conclusive evidence was lacking. An authentic sample of the 1,2 addition product 4 (IR (neat) 3450 cm^{-1} ; NMR (δ^{CCl_4}) 5.70 (2H, br s), 0.00 (9H, s)) was therefore prepared as outlined below



and its lithium salt was subjected to the same conditions used for the conjugate addition reaction. We found no equilibration to 3-trimethylsilyl-2-cyclohexenone. In fact we could not detect any isomerization even after several hours at room temperature. Therefore the reaction of Me_3SiLi with 2-cyclohexenone leads directly to the 1,4 adduct.

The reaction of tert.-butyllithium to 2-cyclohexenone is also an irreversible process. Although isomerization via tert.-butyl radical and cyclohexenone ketyl should be possible, we have been unable to effect anionic rearrangement of 1-tert.-butyl-2-cyclohexen-1-ol to 3-tert.-butylcyclohexanone even using potassium hydride and 18-crown-6 in refluxing THF.⁴ We have however found a particularly interesting solvent effect on the site of the reaction of Me_3ClLi with 2-cyclohexenone. As outlined below, the amount of 1,4 addition is roughly proportional to the basicity of the reaction medium. These results do not appear to be due to solvent impurities since other organolithium reagents gave much less conjugate addition. For example, *n*-butyllithium gives only 20% 1,4 addition



| | | | |
|----------|-----------------------------|------|-----|
| Solvent: | Et ₂ O | 100% | - |
| | THF | 95% | 5% |
| | THF + 5% HMPA | 65% | 35% |
| | THF + 20% HMPA ⁵ | 10% | 90% |

in 20% HMPA-THF while methyl lithium reacts exclusively via the 1,2 mode in the same solvent.

It is interesting that these new results are qualitatively opposite to expectations based on HSAB theory.⁶ It would be predicted that softer nucleophiles toward the bottom of the periodic table ($\text{Me}_3\text{Sn}^- \rightarrow \text{Me}_3\text{Si}^- \rightarrow \text{Me}_3\text{C}^-$) would add preferentially to the softer of two electrophilic sites ($\text{C}=\text{C}=\text{C}=\text{O}$). As described above it was found that in ionizing solvents where counterion effects would be minimized, the soft trimethylstannyl anion adds kinetically to the hard carbonyl while the harder trimethylcarbon anion adds largely to the softer β -olefinic site. Although HSAB behavior may play a role in determination of the site of nucleophilic additions to enones, our results are better explained kinetically by the principle that direct nucleophilic additions are generally 1,2 and electron transfer additions are generally 1,4 processes.⁷ These generalities are of course subject to overriding steric and electronic effects. Considering the carbanion additions, the tert.-butyl anion is known to be much less stable than the corresponding radical. Since the electrode potentials for oxidation of Me_3C^- and for reduction of 2-cyclohexenones are roughly -2.6^8 and -2.1^9 volts (vs. SCE) respectively, electron transfer by tert.-butyl anion to 2-cyclohexenone is a thermodynamically favorable process and should lead to kinetic 1,4-addition.¹⁰ In contrast the methyl anion is more stable than the methyl radical. Thus electron transfer should not be favorable and 1,2 addition of methyl lithium would be the expected result.¹¹ Although the oxidation potential of Me_3Si^- does not appear to have been measured, a great many of its reactions have been rationalized in terms of prior electron transfer.^{3,12} In the case of the trimethylstannyl reactions, the great stability of the radical and the anion¹³

should thermodynamically disfavor electron transfer processes¹⁴ relative to Me₃C⁻ and Me₃Si⁻ and thus lead to a direct nucleophilic 1,2 addition.

Notes and References:

1. W.C. Still, *J. Am. Chem. Soc.*, **99**, 4836 (1977).
2. The amount of 2 varied from 60-80% depending on temperature control and the speed of enone addition and quenching. We believe that partial equilibration may have occurred during the addition of the reagents.
3. W.C. Still, *J. Org. Chem.*, **41**, 3063 (1976).
4. Cf. D.A. Evans and A.M. Golob, *J. Am. Chem. Soc.*, **97**, 4765 (1975); S.R. Wilson, D.T. Mao, K.M. Dernberg and S.T. Ezmirly, *Tetrahedron Lett.*, 2559 (1977); B. Franzus, M. Sheinbaum, D.L. Waters and H.B. Bowlin, *J. Am. Chem. Soc.*, **98**, 1241 (1976); R.W. Thies, E. P. Seitz, *J. Chem. Soc., Chem. Commun.*, 846 (1976).
5. Under these conditions there was a substantial amount of organometallic decomposition. The decomposition could be minimized by adding tert.-butyllithium to a solution of 2-cyclohexenone in THF/HMPA; however, the ratio of 1,2 to 1,4 addition dropped to unity.
6. Reviews: B. Saville, *Angew. Chem. Int. Ed.*, **6**, 928 (1967); R. G. Pearson, *J. Chem. Ed.*, **45**, 581, 643 (1968); T.-L. Ho, *Chem. Rev.*, **75**, 1 (1975).
7. Other kinetic 1,4-addition processes are believed to proceed by prior electron transfer; cf., *inter alia*: H.O. House, "Modern Synthetic Reactions", 2nd ed., Benjamin, Menlo Park, Calif., 1972, pp 173-205; G.H. Posner, *Org. React.*, **19**, 1 (1972); H.O. House, *Accnts. Chem. Res.*, **9**, 59 (1976).
8. R. Breslow and R. Goodin, *J. Am. Chem. Soc.*, **98**, 6076 (1976).
9. H.O. House and M.J. Umen, *J. Am. Chem. Soc.*, **94**, 5495 (1972); H.O. House, L.E. Huber and M.J. Umen, *ibid.*, **94**, 8471 (1972).
10. Cf. W.A. Nugent, F. Bertini and J.K. Kochi, *J. Am. Chem. Soc.*, **96**, 4945 (1974); H.O. House and P.D. Weeks, *ibid.*, **97**, 2785 (1975).
11. Methylolithium may add in the 1,4 sense to α,β -enones if the β -carbon is much less hindered than the carbonyl, e.g. J.E. Ellis, J.S. Dutcher and C.H. Heathcock, *J. Org. Chem.*, **41**, 2670 (1976).
12. H. Sakurai, A. Okada, H. Umino and M. Kira, *J. Am. Chem. Soc.*, **95**, 955 (1973); H. Sakurai, H. Umino and A. Okada, *Chem. Lett.*, 671 (1973).
13. H. Gilman, O.L. Marrs, W.J. Trepka and J.W. Diehl, *J. Org. Chem.*, **27**, 1260 (1962). The relatively high acidity of R₃SnH also attests to the stability of the stannyl anion.
14. Evidence for partial electron transfer in the alkylation of trimethylstannylolithium was recently reported: P.J. Krusic, P.J. Fagan and J. San Filippo, *J. Am. Chem. Soc.*, **99**, 250 (1977).