

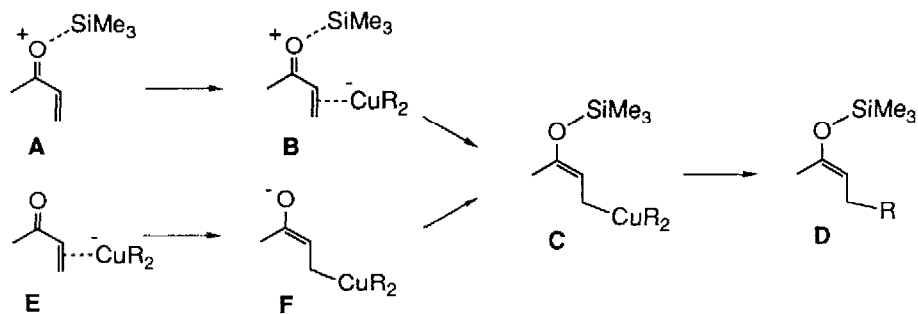
DOES Me_3SiCl ACTIVATE CONJUGATE ADDITION OF COPPER REAGENTS AS A LEWIS ACID ?

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Summary: The role of Me_3SiCl to accelerate the conjugate addition of organocopper reagents has been examined by comparison of the stereochemical results of reactions with 6- and 2,6-disubstituted cyclohexenones, and mechanism involving an initial coordination of the chlorosilane to enones has been proposed.

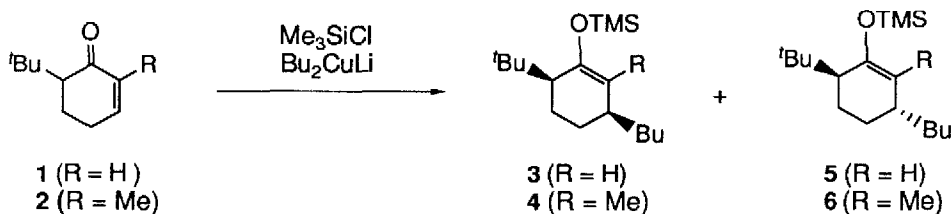
Me_3SiCl accelerated conjugate addition of copper reagents has emerged to be a reliable tool in organic synthesis.¹⁾ The principle of the acceleration by Me_3SiCl has still been unclear, but is of great interest since such mechanistic background may provide several synthetic advantage of new characteristics which lacks in the former organocopper chemistry. There are two plausible rationales to account for the significant rate enhancement with Me_3SiCl . One relates to the very early stage of the reaction, where coordination of Me_3SiCl as a Lewis acid with the substrate (A) to lower the enone LUMO is assumed.^{1c)} The other postulates that Me_3SiCl simply traps the enolate intermediate (F - C) to drive the equilibrium to product formation.^{1a)}



In order to differentiate these two possibilities, we investigated conjugate addition of dibutylcopper lithium either in the presence or absence of Me_3SiCl , using enones **1** and **2** as probes. The reactions were performed as follows: **Method A** (with Me_3SiCl); the enone was treated with Bu_2CuLi (1.2 eq) and Me_3SiCl (5 eq) in THF at -78°C , and **Method B** (without Me_3SiCl); the enone was treated with Bu_2CuLi (1.2 eq) in THF at -78°C -- -40°C . After disappearance of the starting enone, the resulting enolate was trapped with $\text{Me}_3\text{SiCl}/\text{HMPA}$.

A tremendous effect of Me_3SiCl was observed on the stereochemical outcome of the addition product. Without Me_3SiCl , both **1** and **2** gave *cis* adducts exclusively (entry 2, 4), while the *trans* adducts were formed predominantly in the presence of Me_3SiCl (entry 1,3). Especially, the complete reversal of the stereoselection (2:98/98:2) in the case of **2** (entry 3, 4) should be remarkable. Since it is unlikely that Me_3SiCl alters the direction of the approach of copper reagents from axial to equatorial, the reverse stereoselection should be the

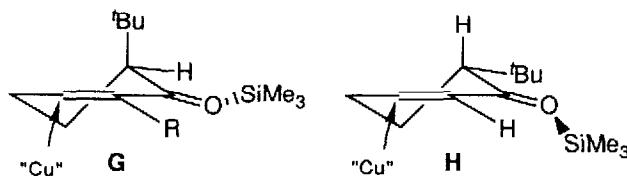
result of different orientation of the 6-*t*butyl group in the stereo-determining step. Namely, Me_3SiCl selectively accelerates an axial attack to the 6-*t*butyl axially oriented enones to give the *trans* adducts. On the other hand, addition of the cuprate takes place preferentially on the 6-*t*butyl equatorial enones to afford the *cis* adducts.



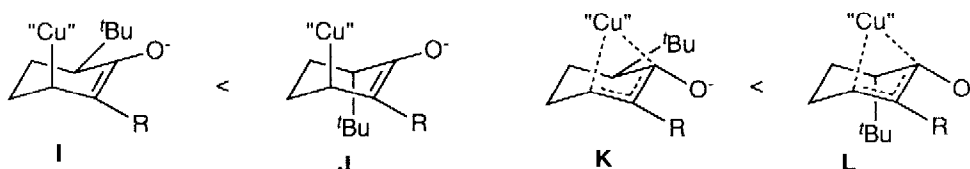
Entry	R	Method	Yield, %	<i>cis:trans</i>
				(3:5)
1	H	A	91	42:58
2	H	B	77	94:6

				(4:6)
3	Me	A	98	2:98
4	Me	B	80	98:2

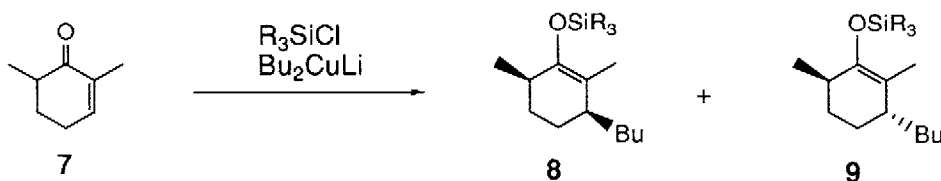
It is known that coordination of Lewis acids toward substrates alters the steric environment around the reaction center to follow the different stereochemical reaction pathway from those in the absence of Lewis acids.²⁾ The reversal of stereochemistry can be well understood providing that the conjugate addition would proceed *via* the Me_3SiCl -activated enone like **A**. The *cis* selection in the Me_3SiCl free reaction can be attributed to the well established axial attack of the copper reagent to enones with the equatorial 6-*t*butyl group, while in the Me_3SiCl -promoted reaction the steric factors of Me_3SiCl /enone complexes to which irreversible conjugate addition of copper reagents would occur seem to be important. Among the plausible Me_3SiCl /enone complexes which might exist in very low concentration,³⁾ complex **G** seems to be the most favored. Though the axial *t*butyl in **G** appears to be disadvantageous, the other complexes must suffer from much more severe steric repulsion between Me_3Si ^{4,5)} and 2-R group (especially methyl) or 6-*t*butyl. The decreased *trans* selectivity in entry 1 is due to the contribution of syn-complex **H** (Me_3Si syn to the double bond).



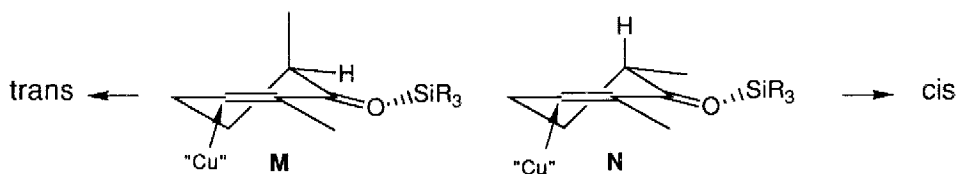
These stereoselectivities are not understood on the basis of the enolate intermediate/ Me_3SiCl trap mechanism.^{1a)} Assuming the enolate intermediate/ Me_3SiCl trap mechanism, the stereochemistry would be kinetically controlled at the stage where the copper reagent irreversibly attacks the enone. The *trans* selection of the Me_3SiCl -mediated reaction might be attributable to the steric repulsion between the 6-*t*-butyl and the copper reagents in **I** (or **K** in d,π^* -complex model⁶⁾). However, this mechanism fails to account for the significant effect of the 2-substituent on the stereoselectivity.



Conjugate addition to 6-methyl derivative **7** was also examined under similar reaction conditions. The results can be explained based on the Lewis acid mechanism. R_3SiCl /enone complex **N** stable comparably to complex **M** would lead to the *cis* adducts **8** (entry 5, 6). Bulkier ethyl group would disfavor the complex **N**, resulting in preferable formation of the *trans* adducts **9** (entry 7).



Entry	R_3SiCl	Yield, %	8 : 9
5	None	49	83:17
6	R = Me	73	56:44
7	R = Et	90	40:60



Thus, the results obtained above support that Me_3SiCl activates conjugate addition of copper reagents as a Lewis acid, playing an important role on the determination of stereochemical outcome.

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References and Notes

- 1) (a) E. J. Corey and N. W. Boaz, *Tetrahedron Lett.*, **1985**, *26*, 6015, 6019. (b) A. Alexakis, J. Berlan, and Y. Besace, *Tetrahedron Lett.*, **1986**, *27*, 1047. (c) Y. Horiguchi, S. Matsuzawa, E. Nakamura, and I. Kuwajima, *Tetrahedron Lett.*, **1986**, *27*, 4025. E. Nakamura, S. Matsuzawa, Y. Horiguchi, and I. Kuwajima, *Tetrahedron Lett.*, **1986**, *27*, 4029. S. Matsuzawa, Y. Horiguchi, E. Nakamura, and I. Kuwajima, *Tetrahedron*, **1989**, *45*, 349. (d) J. Enda and I. Kuwajima, *J. Am. Chem. Soc.*, **1985**, *107*, 5495. (e) C. R. Johnson and T. J. Marren, *Tetrahedron Lett.*, **1987**, *28*, 27.
- 2) K. Maruoka, T. Itoh, M. Sakurai, K. Nonoshita, and H. Yamamoto, *J. Am. Chem. Soc.*, **1989**, *110*, 3588. Y. Matsumura, K. Maruoka, and H. Yamamoto, *Tetrahedron Lett.*, **1982**, *23*, 1929.
- 3) A support on formation of such Me_3SiCl /enone complexes is lacking; namely ^1H NMR measurement for a mixture of cyclohexenone and Me_3SiCl failed to detect the Lewis acid/Lewis base complex; see ref 1a and 1c.
- 4) In addition, the lower basicity of syn lone pair (to the C-C double bond) might make the syn complexes less important. For the basicity of lone pairs of enone carbonyls, see: P. M.-Rust and P. Glusker, *J. Am. Chem. Soc.*, **1984**, *106*, 1018.
- 5) The validity of this discussion was confirmed by performing a conjugate addition of a silyl ketene acetal toward **2**, of which mechanism is apparent.⁷⁾ When **2** was treated with trimethylsilyl enol ether of ethyl isobutyrate in the presence of cat. TASF (THF, -70 -- -45 °C, 4 h), *cis* adduct was the major product (86%, *cis:trans* = 79:21). TMSOTf catalyzed reaction (CH_2Cl_2 , -70 °C--rt, 18 h) which proceeds *via* coordination of Lewis acidic TMS group on the carbonyl oxygen, however, predominantly gave the *trans* adduct (90%, *cis:trans* = 10:90).
- 6) E. J. Corey, F. J. Hanon, and N. W. Boaz, *Tetrahedron*, **1989**, *45*, 545.
- 7) Each reaction mechanism is considered to be similar with that of well established aldol reaction of enol silyl ethers with aldehydes. For fluoride catalyzed reactions: I. Kuwajima, E. Nakamura, and M. Shimizu, *J. Am. Chem. Soc.*, **1982**, *104*, 1025. R. Noyori, I. Nishida, and J. Sakata, *ibid.*, **1983**, *105*, 1598. For TMS-OTf catalyzed reactions: S. Murata, M. Suzuki, and R. Noyori, *ibid.*, **1980**, *102*, 3248.

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