Effect of TMSCl on the Conjugate Addition of Organocuprates to α-Enones: A New Mechanism[1a,b]

Steven H. Bertz,*[1c] Guobin Miao,[1d]
Bryant E. Rossiter,†[1d] and James P. Snyder*[1e]

Lonza Inc., Annandale, New Jersey 08801
Chemistry Department, Brigham Young University
Provo, Utah 84602
Chemistry Department, Emory University
Atlanta, Georgia 30322

Received February 14, 1995

Following the remarkable observations by Corey and Boaz that chlorotrimethylsilane (TMSCl) could change both the rate and the stereochemistry of organocuprate reactions,[2] several groups studied this effect.[3] Most subsequent investigators also used a nucleophilic additive, such as hexamethylphosphoramide (HMPA),[3b,c,f,g] 4-(dimethylamino)pyridine (DMAP),[3c] or tetramethylethylenediamine (TMEDA),[3e] and several reported the isolation of TMS enol ethers.[3b−e] Corey et al. proposed a mechanism in which the TMSCl directly silylates the O of the enone in a "d,π*-complex".[2] Heretofore, no one has made a special attempt to determine whether the TMS enol ethers were formed directly or by subsequent silylation of the corresponding enolates, although one group hinted the latter.[3a]

Our interest in this subject was rekindled by the suggestion of Lipshutz et al. that the Cl atom of the TMSCl molecule is coordinated by the lithium of the cuprate, and that this complex is an intermediate in the TMSCl-assisted reaction of organocuprates with α-enones.[4] The other salient feature of the proposed mechanism is the formation of the TMS enol ether directly via a cyclic intermediate. We have executed careful experiments on a cuprate−TMSCl−enone system and carried out density functional theory (DFT) calculations, and we propose a new model that is consistent with both the experimental evidence and the theoretical results.

For the representative cuprate, we chose $Bu_2CuLi\cdot LiI$,[5] which was also studied by Corey,[2] Kuwajima,[3d] and Lipshutz.[4] In connection with previous NMR work,[6a−c] we added HMPA to organocuprates in aliquots of 1 equiv; almost all of the effect on the chemical shift was observed when 3 equiv of HMPA/Li had been added.[7a] Therefore, we use 6 equiv of HMPA/$R_2CuLi\cdot LiI$ and 6 equiv of TMSCl, so that [TMSCl] = [HMPA].[7b]

Chemical yields for reactions of $Bu_2CuLi\cdot LiI$ with 2-cyclohexenone (**1**) are summarized in Table 1.[8] Without additives (entries 1−4), yields of 3-butylcyclohexanone (**2**) obtained at −78 °C are consistently higher in ether than in THF at the same times.[9] Yields of **2** obtained in the presence of HMPA alone were uniformly low (e.g., 24% in ether and 19% in THF after 1 h at −78 °C); therefore, they were not included in Table 1.

Table 1. Yields (%) of **2** and **3** from **1** and $Bu_2CuLi\cdot LiI$[a]

		ether		THF	
additive	time (h)[b]	**2**	**3**	**2**	**3**
1. none[c]	1	66		47	
2. none[c]	0.1	67		45	
3. none[c]	0.01	69		46	
4. none[c]	0.001	54		40	
5. TMSCl[d]	1	67	24	34	62
6. TMSCl[d]	0.1	80	15	43	52
7. TMSCl[d]	0.01	84	13	65	35
8. TMSCl[d]	0.001	95	2	72	27
9. TMSCl + HMPA[e]	1	14	82	5	92
10. TMSCl + HMPA[e]	0.1	12	84	10	81
11. TMSCl + HMPA[e]	0.01	11	86	11	84
12. TMSCl + HMPA[e]	0.001	17	80	14	85

[a] **1**, 2-cyclohexenone; **2**, 3-butylcyclohexanone; **3**, TMS enol ether of **2**. [b] 1 h = 60.0 min, 0.1 h = 6.0 min, 0.01 h = 36 s, and 0.001 h = 4 s. [c] Reactions quenched with 3 mL of saturated aq $NaHCO_3$ at −78 °C. [d] Six equivalents. Reactions quenched with HMPA (6 equiv) and pyridine (3 equiv in ether, 1 equiv in THF), followed by 3 mL of saturated aq $NaHCO_3$ after 4 s, all at −78 °C. [e] Six equivalents each. Reactions quenched with pyridine (3 equiv in ether, 1 equiv in THF), followed by 3 mL of saturated aq $NaHCO_3$ after 4 s, all at −78 °C.

When TMSCl (6 equiv) is added to the cuprate in ether 0.1 h before the enone, all at −78 °C, the ratio of percent yields of **2**:**3** after the shortest time (4 s, entry 8) is 95:2. After 1 h, the amount of TMS enol ether **3** increases to 24% (entry 5), which can be attributed to silylation of the enolate. When **1** was added to the cuprate first and stirred for 0.1 h to generate the enolate, the addition of TMSCl gave percent yields of **2**:**3** of 100:<0.1 after 4 s and 81:16 after 1 h at −78 °C. It is clear that with TMSCl alone, the initial product at −78 °C is enolate **4**, and that the **3** observed arises from its subsequent silylation.

Careful control experiments established that TMS enol ether **3**, prepared according to the Swedish recipe,[10a] was stable under the workup conditions.[8b] Efficacy of the quench conditions is vouchsafed by the observation that yields of **3** as high as 86% are obtained in ether (entry 11) and 92% in THF (entry 9).[10b]

With TMSCl (6 equiv) in THF, the yield of **3** increases from 27% to 62% over the course of 1 h at −78 °C (entries 8→5).

---

† Deceased 1995.

(1) (a) New Copper Chemistry. 25. For part 24, see ref 15. For part 23, see: Bertz, S. H.; Vellekoop, A. S.; Smith, R. A. J.; Snyder, J. P. *Organometallics* **1995**, *14*, 1213. (b) Abstracted in part from Miao, G. Ph.D. Dissertation, Brigham Young University, Provo, UT, 1995. (c) Lonza, Inc. (d) Brigham Young University. (e) Emory University.

(2) (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015. (b) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6019. (c) Corey, E. J.; Hannon, F. J.; Boaz, N. W. *Tetrahedron* **1989**, *45*, 545.

(3) (a) Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047. (b) Horiguchi, Y.; Matsuzawa, S.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4025. (c) Nakamura, E.; Matsuzawa, S.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4029. (d) Horiguchi, Y.; Komatsu, M.; Kuwajima, I. *Tetrahedron Lett.* **1989**, *30*, 7087. (e) Johnson, C. R.; Marren, T. J. *Tetrahedron Lett.* **1987**, *28*, 27. (f) Bertz, S. H.; Dabbagh, G. *Tetrahedron* **1989**, *45*, 425. (g) Bertz, S. H.; Smith, R. A. J. *Tetrahedron* **1990**, *46*, 4091.

(4) Lipshutz, B. H.; Dimock, S. H.; James, B. *J. Am. Chem. Soc.* **1993**, *115*, 9283.

(5) Corey, E. J.; Posner, G. H. *J. Am. Chem. Soc.* **1968**, *90*, 5615.

(6) (a) Bertz, S. H.; Dabbagh, G.; He, X.; Power, P. P. *J. Am. Chem. Soc.* **1993**, *115*, 11640. (b) Bertz, S. H. *J. Am. Chem. Soc.* **1991**, *113*, 5470. (c) Bertz, S. H. *J. Am. Chem. Soc.* **1990**, *112*, 4031. (d) Bertz, S. H.; Smith, R. A. J. *J. Am. Chem. Soc.* **1989**, *111*, 8276. (e) Bertz, S. H.; Dabbagh, G.; Mujsce, A. M. *J. Am. Chem. Soc.* **1991**, *113*, 631.

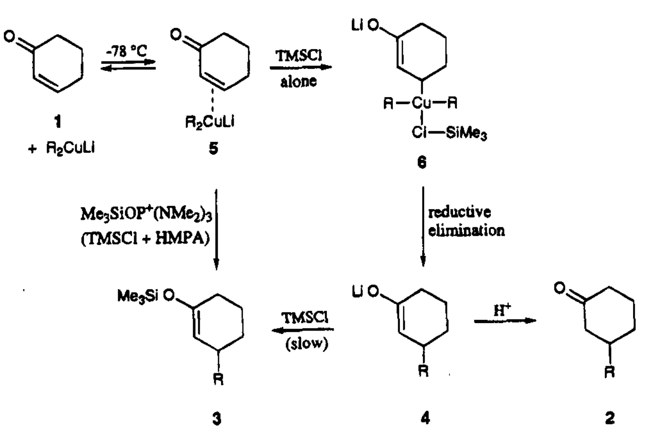
(7) (a) LiI and LiBr are contact ion pairs in THF and show similar behavior: Reich, H. J.; Borst, J. P.; Dykstra, R. R.; Green, D. P. *J. Am. Chem. Soc.* **1993**, *115*, 8728. (b) Several workers have used 5 equiv of TMSCl (refs 2, 3d).

(8) (a) General procedure for conjugate addition reactions using organocuprate reagents in the presence of additives: A 4-dram vial was charged with CuI (190 mg, 1.00 mmol), equipped with a magnetic stir bar, filled with Ar, and sealed with a rubber septum. Dry diethyl ether or THF (4.0 mL, distilled from Na/benzophenone) was added via syringe under Ar. The suspension was cooled to −78 °C, and BuLi (0.82 mL, 2.44 M in hexane, 2.00 mmol) was added. The reaction mixture was stirred for 6 min at −78 °C and then annealed for 6 min at 0 °C (ref 8c). The resulting solution was cooled to −78 °C, and 0.76 mL (6.0 mmol) of TMSCl was added in 1 mL of solvent, followed by 1.04 mL (6.0 mmol) of HMPA in 1 mL of solvent in some cases. After 6 min at −78 °C, a mixture of 2-cyclohexen-1-one (0.100 mL, 1.00 mmol) and dodecane (0.100 mL, internal standard) was added in 1 mL of solvent. After being stirred at −78 °C for the appropriate time, the reactions were quenched as described below, and the organic layers were dried over Na_2SO_4. The THF solutions were diluted with an equal volume of ether. The yields of **2** and **3** were determined by GC analysis. (b) When quenching ethereal solutions, it is not sufficient that the pH be slightly basic. For the best results in ether, 3 equiv of pyridine must be added; 6 equiv of HMPA must also be added to those reaction mixtures which do not contain it already. Thus, an organocuprate reaction mixture in ether that has been treated with 6 equiv of TMSCl is quenched by adding 3 equiv of pyridine and 6 equiv of HMPA in 0.5 mL of ether, and then 3 mL of saturated aqueous $NaHCO_3$ after 4 s. In THF, 1 equiv of pyridine is sufficient. Control experiments demonstrate that both **2** and **3** are stable under these conditions. (Cf. ref 10b.) (c) Bertz, S. H.; Gibson, C. P.; Dabbagh, G. *Tetrahedron Lett.* **1987**, *28*, 4251.

(9) (a) Coordinating solvents such as THF and HMPA retard the reactions of cuprate reagents with α-enones: House, H. O.; Respess, W. L.; Whitesides, G. M. *J. Org. Chem.* **1966**, *31*, 3128. (b) Hallnemo, G.; Ullenius, C. *Tetrahedron* **1983**, *39*, 1621. (c) Also with tosylates: Johnson, C. R.; Dutra, G. A. *J. Am. Chem. Soc.* **1973**, *95*, 7783.

0002-7863/95/1517-11023$09.00/0

Scheme 1



It should be noted that the mass balances are very good (95%–100%). Addition of TMSCl to the enolate (generated as above) gave percent yields **2**:**3** of 99:0.3 after 4 s and 32:66 after 1 h at −78 °C. (The silylation of enolates is generally faster in THF than in ether.[11]) Thus, silylation occurs predominately after enolate formation; however, approximately a quarter of the product at −78 °C may be due to direct silylation of a Cu–enone complex (vide infra).

The addition of both TMSCl and HMPA (6 equiv of each) to the cuprate before **1** in ether or THF gives a high yield of **3** (80% or 85%, respectively) after the shortest time we can reproducibly attain (4 s, entry 12). To rule out fast silylation of the enolate with TMSCl/HMPA at −78 °C, the enolate was generated as described above, and then a mixture of TMSCl and HMPA (6 equiv of each) was added. The yields of TMS enol ether **3** after 4 s at −78 °C were 0.1% in ether and 0.7% in THF, after the usual workup.[8b] (The corresponding yields of **2** were 100% and 99%, respectively.) Consequently, a species that appears before the enolate on the reaction coordinate is intercepted by TMSCl/HMPA. It should be noted at this point that neither the Lipshutz[4] nor the Corey[2] mechanism includes HMPA, as it was not included in their reaction mixtures.

Corey et al. proposed that "the acceleration of the conjugate addition of cuprates to α,β-enones by chlorotrimethylsilane is due to silylation of the d,π^*-complex to generate the enol silyl ether of a Cu(III) β-adduct rather than electrophilic activation of the enone by the chlorosilane." [2c] While they draw a π-allyl intermediate which undergoes silylation,[2a] we note that the π-olefin complex (**5**, Scheme 1) also has significant electron density on O and could be silylated instead at low temperature. In contrast to previous reports,[2,3d] in our system it appears that TMSCl alone is not able to silylate the cuprate–enone complex in ether and is able to silylate it only to a limited extent (~25%) in THF. The formation of a more reactive silylating agent $(CH_3)_3SiOP^+[N(CH_3)_2]_3$ is well precedented,[12] and may explain the direct formation of **3** from **5** with TMSCl + HMPA.

When the 0.1 h reaction mixtures containing TMSCl (cf. entry 6) were allowed to warm to 0 °C and quenched after 1 h, the ratios of percent yields of **2**:**3** were 9:87 and 5:95 for ether and THF, respectively. Much of the confusion concerning this mechanistic problem arises because it is common practice to warm such reaction mixtures above −78 °C before quenching.

Based on the above results, we conclude that the Lipshutz mechanism in which the TMS enol ether is formed directly via a cyclic intermediate or transition state can be ruled out. Even if complexation of TMSCl by some organocopper reagents exists in the ground state—as first reported by Nilsson[13]—there is no evidence that it is crucial to the course of cuprate reactions.

What, then, is the mechanism whereby TMSCl influences the rate and stereochemistry of organocuprate reactions? We believe that the Cl of TMSCl attacks the Cu in **5** to give the key intermediate **6** (Scheme 1). This complexation also stabilizes the transition state for subsequent reductive elimination. It may be noted that a bridging Cl atom places the Si in the β-position relative to Cu(I), in analogy with β-silylcarbenium ions and the siloxyphosphonium ion discussed above.

To explain the stereochemistry of their $(CH_3)_3SiI$ results, Olsson et al. proposed an intermediate in which the I was coordinated to the Cu, and the Si to the O of a Cu–enone π-complex.[10a,14] Cuprate–enone π-complexes such as **5** are well characterized.[6d] A square-planar intermediate analogous to **6** was proposed by Johnson et al. to explain substitution results with tosylates[9c] and by Bertz et al. with iodoalkanes.[6e]

Initial theoretical study of the mechanism of TMSCl-assisted organocuprate addition involved performing DFT geometry optimizations with pseudopotentials on copper (B3LYP/LANL2DZ)[15] for complexes containing TMSCl. First, the chlorine in $(CH_3)_3SiCl$ was placed 2.5 Å from the trigonal metal atoms of the anions $[(CH_3)_2M{-}ClSi(CH_3)_3]^-$ (M = Li, Cu), followed by energy minimization of the aggregate. The chlorosilane drifts away from both anions and they become linear, as the total energies decrease monotonically to the dissociation limit. These results suggest that the Cl of TMSCl does not form a productive interaction with Li (or Cu) in the Gilman dimer.

On the other hand, T-shaped Me_3Cu, a computationally accessible model for **6**, was recently predicted to associate with ethereal solvent.[16,17] We find that it likewise associates with TMSCl to give a stationary point with an energy gain of 4.3 kcal/mol relative to optimized precursors. An activation energy of 3.2 kcal/mol is calculated for reductive elimination of ethane from $(CH_3)_3CuClSi(CH_3)_3$. On the other hand, substitution of HMPA for TMSCl gives a species $(CH_3)_3CuOP[N(CH_3)_2]_3$ that is considerably more stable (34.7 *vs* 4.3 kcal/mol) and has a higher barrier to reductive elimination (10.1 *vs* 3.2 kcal/mol).

We propose that TMSCl enhances the rate of cuprate addition by promoting conversion of the initially formed π-complex (e.g., **5**, Scheme 1) to a reactive tetravalent copper species (**6**)[16] capable of rapid reductive elimination to product (**4**). The key observation is that TMSCl stabilizes the transition state more than it does the ground state (lower activation energy), whereas HMPA stabilizes the ground state more (higher activation energy). Consequently, a unified mechanistic scheme explains both the accelerating effect of TMSCl and the retarding effect of HMPA, as observed here in the same system for the first time.

In summary, silylating agents can influence organocopper reactions in two fundamentally different ways: strong silylating agents (e.g., TMSCl + HMPA, TMSOTf[3g]) can directly silylate an intermediate Cu–enone complex. Relatively weak silylating agents (e.g., TMSCl, TMSI[3g,14]) may stabilize the transition state for reductive elimination by complexation that places Si β to Cu. The use of TMSX (or, more generally, β-Si) to stabilize high formal oxidation states may be expected to be a general principle for organometallic chemistry.

Acknowledgment. We thank Paul Hudrlik (Howard University) for a particularly helpful discussion concerning the hydrolysis of TMS enol ethers and Martin Nilsson (Chalmers University) for useful references and helpful feedback. J.P.S. thanks Dennis Liotta and Keiji Morokuma (Emory University) for their generous hospitality.

JA950518G

---

(10) (a) Bergdahl, M.; Eriksson, M.; Nilsson, M.; Olsson, T. *J. Org. Chem.* **1993**, *58*, 7238. (b) Triethylamine has also been used, and it was reported that "A small amount of desilylated material invariably occurred by this procedure." See: Matsuzawa, S.; Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Tetrahedron* **1989**, *45*, 349.

(11) Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4462, 4464.

(12) Bassindale, A. R.; Stout, T. *Tetrahedron Lett.* **1985**, *26*, 3403.

(13) Lindstedt, E.-L.; Nilsson, M.; Olsson, T. *J. Organomet. Chem.* **1987**, *334*, 255.

(14) Bergdahl, M.; Lindstedt, E.-L.; Olsson, T. *J. Organomet. Chem.* **1989**, *365*, C11.

(15) For a description of the methods used, see: Snyder, J. P.; Bertz, S. H. *J. Org. Chem.* **1995**, *60*, 4312.

(16) Snyder, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 11025.

(17) Dorigo, A. E.; Wanner, J.; Schleyer, P. v. R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 476.