

Reactive Enolates from Enol Silyl Ethers

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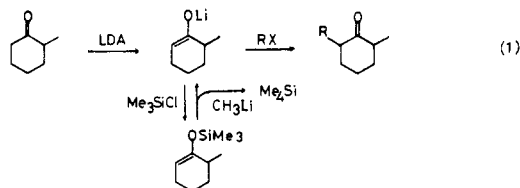
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Among a number of reactive intermediates in organic chemistry, enolate anions may claim to be one of the most important for achieving C-C bond formation.¹ Enolates are usually generated by the action of a base upon a carbonyl compound possessing acidic α -protons. Cyclohexanone and potassium *tert*-butoxide have been a standard textbook combination, the latter representing a typical conventional base. This base generates an enolate anion under a thermodynamic equilibrium, because *tert*-butyl alcohol, the conjugate acid, is as acidic as the ketone substrates.

Development of "modern" enolate chemistry, brought about by the availability of nonnucleophilic strong lithium bases (e.g., lithium diisopropylamide, LDA)^{2,3} has been dramatic and its influence far-reaching. The real synthetic potential of enolate anions has thus become fully appreciated through the growth of new technology to generate "clean" enolates under kinetically controlled conditions.

In order to facilitate the reader's understanding of the problems in enolate chemistry, it may be useful to discuss briefly the regiochemistry of ketone enolate formation. Let us take as an example the alkylation of 2-methylcyclohexanone at the C-6 position (eq 1). For



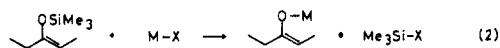
this to be accomplished, one must specifically form the less substituted (and less stable) enolate and then allow this to react with an electrophile before the enolate equilibrates to the more stable isomer. With the aid of a strong lithium amide base (e.g., LDA), one can selectively remove a C-6 methylene proton and use the resulting enolate for a C-C bond-forming reaction.^{1,2} The alkylation reaction in presence of *tert*-butoxide, however, occurs less selectively, favoring the reaction at the C-2 position via the more stable enolate. Under the conventional equilibrating conditions, one must employ extraneous blocking (for C-2) or activating (for C-6) groups, which are to be removed eventually.¹

Isao Kuwajima was born in 1937 and received his B.S. and his Ph.D. from Tokyo Institute of Technology. He joined the Faculty of TIT in 1966, moved to Aoyama Gakuin University as Associate Professor in 1970, and then returned to TIT in 1973, where he is currently Professor of Chemistry. His research interests include exploration of new synthetic methodologies and their application to natural product synthesis.

Eiichi Nakamura was born in Tokyo on February 24, 1951. He received a B.S. degree and a Ph.D. from Tokyo Institute of Technology, under the direction of Isao Kuwajima. After 2 years as a postdoctoral fellow at Columbia University with Gilbert Stork, he returned to TIT as Assistant Professor and was recently appointed Associate Professor of Chemistry. Dr. Nakamura's research interests are centered mainly around synthetic organic chemistry, sometimes covering the field of organometallic chemistry and reaction mechanisms.

Lithium bases thus make a host of kinetically favored (lithium) enolates available to organic chemists. In order for the generation of kinetically unaccessible (but not necessarily thermodynamically more stable) enolates, yet another approach was needed, namely, methods for the temporary storage of the regiochemical (and stereochemical) integrity of the enolate anion. The most successful of the strategies developed for this purpose was put into practice by Stork³ in the late sixties. He demonstrated that an enolate anion can be transformed into an enol silyl ether, purified either by distillation or chromatography, and then converted back to the anion (eq 1). During the course of this sequence both the regio- and the stereochemical features of the starting enolate are retained. A particular merit of the enol silyl ether approach, as revealed later by reports of various workers, stems from the fact that it is available not only from the parent ketone but also from other starting materials through diverse synthetic reactions.⁴

Transformation of the enol silyl ether to the corresponding enolate anion in Stork's original report³ was achieved by the action of methyl lithium at 0 °C, and as a consequence, the method displays an inherently narrow tolerance of functional groups and naturally serves only for the generation of lithium enolates. We felt that it would be desirable to find a milder version of this method that would provide access to enolates other than lithium enolates. This conception has been reduced to practice through the generalized eq 2, and a variety of new reactive enolate species have been generated and characterized. These metathetical routes to reactive enolate species have given a new dimension to enolate chemistry and at the same time to organic syntheses in general.



Fluoride-Mediated Generation of Quaternary Ammonium Enolates

We initiated our work by examining the possibility of generating quaternary ammonium enolates through the action of an ammonium fluoride upon enol silyl ether (cf. eq 2, where X = F).⁵ Our interest in the ammonium enolates was focused not only on their synthetic utility but also on the properties of these anions that possess a large, "soft" counteranion. The

(1) Reviews: House, H. O. "Modern Synthetic Reactions"; W. A. Benjamin: Menlo Park, CA, 1972. d'Angelo, J. *Tetrahedron* 1977, 33, 2977. Mundy, B. P. "Concepts of Organic Chemistry"; Marcel Dekker: New York, 1979; Chapter 9.






(2) House, H. O.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* 1971, 36, 2361.

(3) (a) Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* 1968, 90, 4462, 4464. (b) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* 1969, 34, 2324.

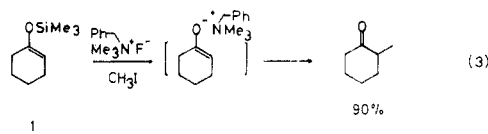
(4) Reviews: Rasmussen, J. K. *Synthesis* 1979, 91. Brownbridge, P. *Synthesis* 1983, 1, 85.

(5) Kuwajima, I.; Nakamura, E. *J. Am. Chem. Soc.* 1975, 97, 3257.

Table I
 Alkylation Reaction

enol silyl ether	RX	% yield
	MeI PhCH ₂ Br BrCH ₂ COOMe BuI	87-91 66-69 72-80 50
	PhCH ₂ Br PhCH=CHCH ₂ Br	72-74 78
	PhCH ₂ Br	59
	BrCH ₂ COOMe	76
	PhCH ₂ Br	59-67

chemistry of such species had been studied in relation to phase-transfer catalysis,⁶ and their reactivities in pure organic solvents^{6b} had been explored much less than those of the (more commonly encountered) metal complexed species.



The extremely high affinity of fluoride anion toward silicon atoms reflects the high homolytic bond energy of the Si-F linkage.⁷ At the time we started these studies, synthetic utilization of this (now well-known) property received prior attention only in connection with the protonolysis of Si-O bonds during removal of silyl protective groups.^{8,9} The major factor that impeded the use of fluoride anion for the generation of nucleophilic species in a stoichiometric sense was the presence of adventitious water in most common fluoride sources. Therefore, unless some precautions were taken to develop an *anhydrous* fluoride source, any nucleophilic species generated during desilylation would be protonated before it might react with a desired electrophile. We were, therefore, gratified to find that molecular sieves can largely remove the water from benzyltrimethylammonium fluoride (BTAF) as indicated by the high-yield production of 2-methylcyclohexanone in the reaction of 1-(trimethylsilyloxy)cyclohexene (1) and BTAF in the presence of methyl iodide (eq 3).^{5,10} Apparently, the fluoride anion reacted with the silicon species much faster than with methyl iodide to generate the expected kind of the enolate anion, which subsequently underwent alkylation. Other halide anions or alkoxide anions did not facilitate similar alkylation reactions. The alkylation reaction proceeded

(6) (a) Starks, C. M.; Liotta, C. "Phase Transfer Catalysis"; Academic Press: New York, 1978. (b) Cf. Zook, H. D.; Gumby, W. L. *J. Am. Chem. Soc.* **1960**, *82*, 1386. Brandstrom, A.; Gustvii, K. *Acta Chim. Scand.* **1969**, *23*, 1215. Review: Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737.

(7) Pauling, L. "The Nature of Chemical Bond", 3rd ed.; Cornell University Press: New York, 1960; Chapter 3.

(8) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

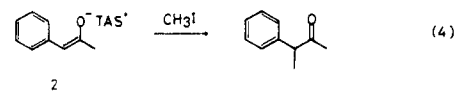
(9) For earlier examples of the generation of nucleophilic species, see: (a) Webb, A. F.; Sethi, D. S.; Gilman, H. *J. Organomet. Chem.* **1970**, *21*, 61. (b) Ishikawa, N.; Isobe, K.-i. *Chem. Lett.* **1972**, 435.

(10) (a) Kuwajima, I.; Nakamura, E.; Shimizu, M. *J. Am. Chem. Soc.* **1982**, *104*, 1025. (b) Kitazume, T.; Ishikawa, N. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2064.

well with a variety of primary alkyl halides (Table I).

Of a number of fluoride sources examined, BTAF proved best for the alkylation reaction. It was later found by Noyori¹¹ that tris(dialkylamino)sulfonium (TAS) fluoride or its Me₃SiF complex is also effective. TAS enolate 2 has been isolated and shown to be a very electron-rich anionic species. The ammonium enolate, which is generated in our reactions albeit in a less pure form, has also been characterized.¹¹

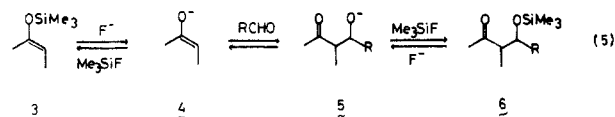
It is interesting to note that despite the expected "nakedness" of the ammonium enolates that aroused our concern about O-alkylation, no sign of this side reaction was found. The TAS enolate 2 also alkylated exclusively on carbon and not on oxygen (eq 4).¹¹ The



reactivities of these metal-free enolates stand in sharp contrast to those of the solvent (HMPA, crown ether, etc.) separated ion pairs of metal enolates (often called "free anions"), which give varying proportions of C- and O-alkylation products.^{2,12} The general absence of either polyalkylated or regiochemically isomeric products adds greatly to the synthetic utility of these fluoride-mediated alkylation reactions.

In retrospect, it was fortuitous that we had employed ammonium fluoride to achieve the generation of metal-free enolates. The fluoride anion turned out to display a remarkable property: it can either be attached readily to a silicon atom or be detached from it under suitable conditions. Having learned this, we then were able to introduce a new, general methodology for organic synthesis: the fluoride-catalyzed reaction of organosilicon compounds. We will illustrate this subject by describing a new aldol reaction.¹³

The aldol reaction is a standard method for the creation of C-C bonds, but its utility in synthesis is severely limited under equilibrating conditions.¹⁴ Several conceptually different approaches to circumvent this problem were devised by the mid-1970s.¹⁵ The aldol reaction that we developed in collaboration with Prof. Noyori's group in Nagoya involved the concept of rapid chemical trapping of the unstable aldol anion 5, which serves to drive the reaction in the forward direction (eq 5).



The aldol coupling of an enol silyl ether and an aldehyde was effected smoothly at low temperatures

(11) (a) Noyori, R.; Nishida, I.; Sakata, J. *J. Am. Chem. Soc.* **1983**, *105*, 1598 and references therein. (b) Noyori, R.; Nishida, I.; Sakata, J. *J. Am. Chem. Soc.* **1981**, *103*, 2106.

(12) Cf. Jackman, J. M.; Lange, B. C. *J. Am. Chem. Soc.* **1981**, *103*, 4494.

(13) (a) Nakamura, E.; Shimizu, M.; Kuwajima, I.; Sakata, J.; Yokoyama, K.; Noyori, R. *J. Org. Chem.* **1983**, *48*, 932. (b) Noyori, R.; Yokoyama, K.; Sakata, J.; Kuwajima, I.; Nakamura, E.; Shimizu, M. *J. Am. Chem. Soc.* **1977**, *99*, 1265. (c) Kleshick, W. A.; Buse, C. T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1977**, *99*, 247. (d) Our recent findings that Me₃SiCl, as well as Me₃SiBr and Me₃SiI, activates carbonyl groups toward nucleophilic attack^{36b} now make us suspect that Me₃SiF has similar properties.

(14) Nielsen, A. T.; Houlihan, W. J. *Org. React.* **1968**, *16*, 1.

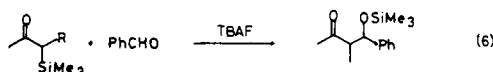
(15) (a) Review: Mukaiyama, T. *Org. React.* **1982**, *28*, 203. (b) House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310.

Table II
Aldol Reaction

enol silyl ether	aldol	% yield
		92
		80
		52 ^a
		48
		69

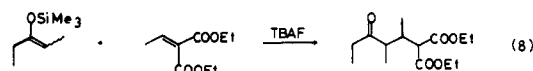
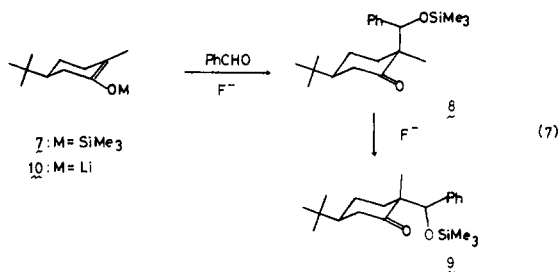
^a Two equivalents fluorotrimethylsilane was added, and only the erythro isomer was formed.

(generally -78 to -20 °C) with less than 0.1 equiv of tetrabutylammonium fluoride (TBAF). For reasons that are obscure, BTAF worked poorly in the aldol reaction. The reaction showed considerable scope with regard to the structures of both reactants (Table II). The reaction was regioselective with respect to the position of the enol double bond in the enol silyl ether. α -Silyl ketones also serve as a source of the enolate anion (eq 6).¹⁶



A number of minor pathways complicated the mechanism of the reaction,¹³ but two principal factors dominate the scene: the overall equilibrium (eq 5) involving the silylated compounds 3 and 6 and the kinetic as well as the thermodynamic relationship between the two anionic species 4 and 5.

The reaction of a conformationally locked substrate 7 (eq 7) was highly instructive in this respect.^{11a,13a} Upon reaction with benzaldehyde for a short time at low temperature using TBAF, 7 gave only an axially attacked adduct 8, whose diastereomeric threo/erythro ratio turned out to reflect thermodynamic control. The



kinetic nature of the axial product formation was readily demonstrated, since 8 slowly isomerized to the more stable equatorial isomer 9 after a prolonged reaction period. It was evident that the equilibration between the enolate 4 and the aldolate 5 is much more

(16) Kuwajima, I.; Inoue, T.; Sato, T. *Tetrahedron Lett.* 1978, 4887. Inoue, T.; Sato, T.; Kuwajima, I. *J. Org. Chem.* 1984, 49, 4671.

Table III
Silylation with ETSA/TBAF^a

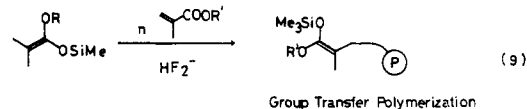
ketone	% yield	% regioselectivity ^b
acetophenone	98	
cyclopentanone	74	
cyclohexanone	98	
cyclooctanone	86	
	90	80:20 ^c
	83	6:94 ^d
	84	99.5:0.5 ^c
	82	86:14

^a Reactions were performed at room temperature with 3–0.5 mol % TBAF in THF. ^b Selectivity between the dotted position and the other. ^c Performed at -78 °C. ^d Performed at room temperature for 2 days.

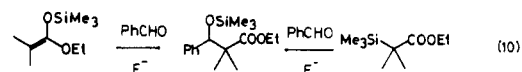
facile (in fact, very much so as found in other instances) than the fluoride-mediated retrograde reaction of the aldol silyl ether 6. The presence of (added) extra Me₃SiF proved advantageous for the increase of the product yield as well as the enhancement of erythro diastereoselectivity.^{11b,13a} It is not improbable that Me₃SiF is acting in such a case as a mild activator of the carbonyl group,^{13d} modifying the major reaction pathway.

Although the aldol reaction of ammonium enolates shown in eq 7 exhibited very much higher axial stereoselectivity than metal-complexed enolates,^{15b} the alkylation reaction (with CD₃I) of the same substrate displayed only moderate selectivity (79% axial) which parallels the selectivity found for the corresponding lithium enolate 10 (83–86%).¹⁰ The reason for such differences in stereoselectivity is presently unclear.

A suitable combination of an enol silyl ether and an unsaturated carbonyl compound results in the Michael reaction (eq 8).^{13a,17} If the structures of the both reactants are similar, polymerization tends to occur, and this has been exploited by Dupont workers for the invention of a new polymerization technique (eq 9).¹⁸



Two forms of silylated esters are readily available: O-silylated and C-silylated ones.⁴ Although both of these reacted smoothly under fluoride catalysis (eq 10), consideration of accessibility and hydrolytic stability made us concentrate on the latter group and, in particular, on ethyl (trimethylsilyl)acetate (ETSA).¹⁹ A









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(18) (a) Webster, W.; Hertler, W. R.; Sogah, D. Y.; Farnham, W. B.; RajanBabu, J. V. *J. Am. Chem. Soc.* 1983, 105, 5706. (b) Sogah, D. Y. "Abstracts", Seventh International Symposium on Organosilicon Chemistry, Kyoto, Sept 9–14, 1984, The Chemical Society of Japan, 3B1400. (c) Sogah, D. Y. U.S. Patent 4 448 980, 1984.

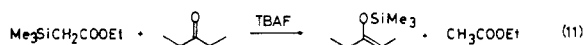
(19) (a) Fessenden, R. J.; Fessenden, J. S. *J. Org. Chem.* 1967, 32, 3535. (b) Gold, J. R.; Sommer, L. H.; Whitmore, F. C. *J. Am. Chem. Soc.* 1945, 70, 2874. (c) Kuwajima, I.; Nakamura, E.; Hashimoto, K. *Org. Synth.* 1983, 61, 122. (d) ETSA is now commercially available from several companies.

Table IV
Selection among Ketones^a

ketone 1		ketone 2		silyln % yield ^b		ratio
		1	2			1:2
		73	0			100:0
		68	11			86:14
		56	34			62:38

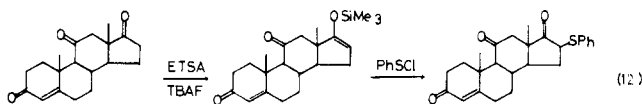
^a The reactions were performed at -78°C with 1 equiv each of ketones 1 and 2 and ETSA. Material balance for each ketone was over 90%. ^b Based each ketone.

major surprise in the reactivities of the enolate derived from ETSA (with 0.1–1 mol % TBAF) was its ability to deprotonate ketones to effect the net transfer of the silyl group from ETSA to the oxygen of the carbonyl partner (eq 11, Table III).^{19c,20} The silylation reaction



applies not only to ketones but to a wide range of acidic substrates (e.g., alcohols and thiols).²² A virtue of ETSA as a silylating reagent is that it leaves volatile ethyl acetate as a single side product. Regioselection of the enol silylation process using ETSA is usually moderate (Table I), but its *Z* stereoselectivity for linear ketones is excellent (eq 11).^{19c,23}

A useful property of the ETSA/TBAF is its ability to react selectively with certain ketone functionality in polyketone substrates according to the acidity of the α -protons.²⁴ Competitive experiments revealed a synthetically useful degree of selectivity (Table IV) as illustrated by a steroidal triketone that could be mono-silylated and then sulfenylated selectively at C-16 (eq 12).



In contrast to the aldol reaction, the silylation reaction proceeds via an autocatalytic mechanism, in which a fluoride anion *initiates* a catalytic cycle involving the enolate of ethyl acetate and that of the substrate.²² The overall reaction (i.e., with respect to the formation of the final silylated product) is not reversible. The regio- and stereochemical features of the reaction indicate, however, that *the transient ammonium enolate of the ketone substrate suffers a rapid equilibration*²⁵ before conversion to the final product.

(20) (a) Nakamura, E.; Murofushi, T.; Shimizu, M.; Kuwajima, I. *J. Am. Chem. Soc.* **1976**, *98*, 2346. (b) Cf. Kita, Y.; Yasuda, H.; Haruta, J.-I.; Sagawa, J.; Tamura, Y. *Synthesis* **1982**, 1089.

(21) Nakamura, E.; Shimizu, M.; Kuwajima, I. *Tetrahedron Lett.* **1976**, 1699.

(22) Nakamura, E.; Hashimoto, K.; Kuwajima, I. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 805.

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(24) Unpublished observation by K. Hashimoto.

(25) Fataftah, Z. A.; Kopka, I. E.; Rathke, M. W. *J. Am. Chem. Soc.* **1980**, *102*, 3959.

Scheme I

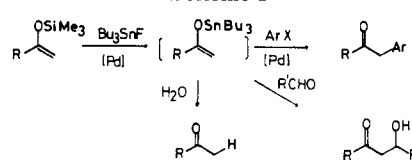
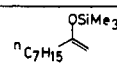
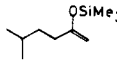
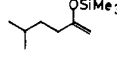
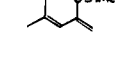
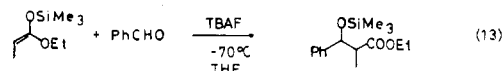


Table V
Palladium-Catalyzed Arylation of Enol Silyl Ethers

enol silyl ether	aryl halide	% yield
	PhBr	65
	<i>o</i> -bromotoluene	59
	<i>p</i> -bromoacetophenone	70
	PhBr	56

If the carbonyl acceptor has no kinetically acidic α -protons available (e.g., benzophenone, aromatic aldehydes, and α,β -unsaturated aldehydes), ETSA undergoes a smooth and irreversible addition reaction.²¹ Such a fluoride-catalyzed Reformatsky reaction of propionate enolate gives an almost 1:1 mixture of diastereomers (eq 13).



A useful variant of the fluoride activation is a highly selective transmetalation from silicon to tin under palladium catalysis (Scheme I).²⁶ The key to this rather unusual transmetalation resides in the fact that the enol silyl ether is activated by the palladium catalyst to facilitate the action of an (apparently) poorly reactive fluoride atom. The tin enolate can either be hydrolyzed by water,²⁷ allowed to undergo aldol reaction,²⁸ or, most importantly, utilized *in situ* for an α -arylation or vinylation reaction (Table V).²⁶ This last reaction represents a relatively rare example of nucleophilic aromatic substitution by an enolate.^{26b} Because the initial transmetalation reaction is highly sensitive to the steric environment of the enol silyl ether, various regioselective transformations are possible.²⁷

The most remarkable feature of these fluoride-promoted reactions is its ability to tolerate a wide variety of functional groups because of the exceedingly high specificity of (mildly basic) fluoride anion for a silicon atom. It has been found that all of the above reactions can be performed in the presence of ethers, epoxides, esters, nitriles, and even ketones.¹⁰

The fluoride-promoted reaction also provides access to acetylide anions.²⁹ The reaction shows a high degree (90%) of axial preference in the reaction with a conformationally locked cyclohexanone (eq 14), implying

(26) (a) Kuwajima, I.; Urabe, H. *J. Am. Chem. Soc.* **1982**, *104*, 6831.

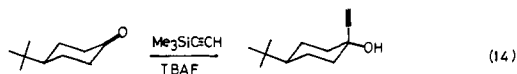
(26) For related works, see: Kosugi, M.; Suzuki, M.; Hagiwara, I.; Goto, K.; Migita, T. *Chem. Lett.* **1982**, 939. Rossi, R. A.; Bunnnett, J. F. *J. Org. Chem.* **1972**, *38*, 1407.

(27) Urabe, H.; Takano, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **1983**, *105*, 5703.

(28) Urabe, H.; Kuwajima, I. *Tetrahedron Lett.* **1983**, *24*, 5001.

(29) (a) Kuwajima, I.; Nakamura, E.; Hashimoto, K. *Tetrahedron* **1983**, *39*, 975. (b) Nakamura, E.; Kuwajima, I. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 498.

that an ammonium acetylide (instead of a hypervalent ethynylsiliconate) is the reactive species.^{29a} Application of the fluoride activation method for the generation of other carbon nucleophiles were subsequently undertaken by Sakurai and Hosomi in their allylsilane chemistry.³⁰



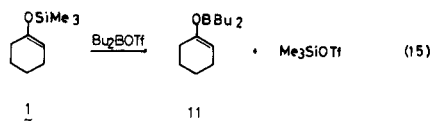
The foregoing paragraphs have surveyed our work and that of others on the generation and the chemistry of new reactive enolate anions; this concept of fluoride activation of organosilicon compounds as a route to nucleophilic species soon received popular support as a standard approach in carbanion chemistry.²⁹⁻³¹ The type of the anionic species generated by the fluoride approach varies from metal-free anions^{11,22,29a} to hypervalent siliconates.^{9b} The very mild and selective nature of fluoride activation is particularly suitable for the initiation of intramolecular reactions.³²

A new development has recently come from the use of bifluoride anion (HF_2^-)¹⁸ instead of fluoride anion. The reported data on bifluoride catalysis, though limited, suggest quite different reactivities for the enolates species obtained in this way (presumed to be pentacoordinated siliconate enolates).¹⁸ For instance, an enol silyl ether undergoes addition to ketones under bifluoride catalysis,^{18c} which sharply contrasts with the results of fluoride catalysis.^{13a}

Preparation and Chemistry of Lewis Acidic Metal Enolates

In the fluoride-promoted reactions, the anionic portion of the M-X compound (eq 2) played a pivotal role and the cationic portion M a subsidiary role. The reaction, that we next explored, involved a reversed situation, in which the M portion plays a significant role.

A new preparative entry to dialkylboron enolates has evolved through the reaction of dibutylboron triflate with enol silyl ether (eq 15). Although this transmetalation reaction looked perfectly reasonable in view of the high affinity of boron and oxygen, it was not obvious whether or not this exchange reaction would proceed to completion. To our delight, the reaction in CCl_4 (or CH_2Cl_2) occurred rapidly (<5 min) and completely at 35 °C to give the boron enolate 11 and trimethylsilyl triflate (Me_3SiOTf) (eq 15), as determined by ^1H NMR.



Our specific interest regarding boron enolates derived from their established importance in aldol chemistry,³⁴

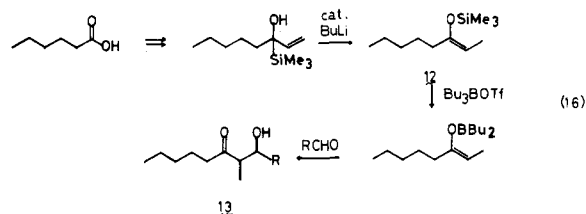
(30) (a) Hosomi, A.; Shirahata, A.; Sakurai, H. *Tetrahedron Lett.* 1978, 3043. (b) DePuy, C. H.; Bierbaum, V. M.; Filippin, L. A.; Grabowski, J. J.; King, G. K.; Schmitt, R. J. *J. Am. Chem. Soc.* 1979, 101, 6443.

(31) For instance: (a) Effenberger, F.; Schollkopf, K. *Angew. Chem., Int. Ed. Engl.* 1981, 20, 265. (b) Corriu, R. J. P.; Perz, R.; Reye, C. *Tetrahedron* 1983, 39, 999. (c) Hiyama, T.; Obayashi, M.; Mori, I.; Nozaki, H. *J. Org. Chem.* 1983, 48, 912.

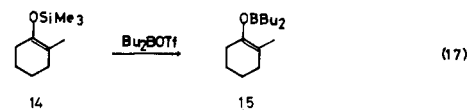
(32) Cf. Vedejs, E.; Martinez, G. R. *J. Am. Chem. Soc.* 1979, 101, 6452. Trost, B. M.; Vincent, J. E. *Ibid.* 1980, 102, 5680. Mejetich, G.; Richard, D.; Casres, A. M. *Tetrahedron Lett.* 1983, 24, 1913.

(33) Kuwajima, I.; Kato, M.; Mori, A. *Tetrahedron Lett.* 1980, 21, 4291.

in which the diastereoselectivity of the reaction of these enolates correlated directly with the geometry of the starting enolate (i.e., erythro from *Z* and threo from *E*) through the alleged chair transition state (TS).³⁴ The boron enolates, however, behaved quite anomalously at first, owing to the presence of Me_3SiOTf in the reaction mixture. Removal of this side product then returned the aldol reaction to its normal course. The merit of our enol silyl ether route to boron enolates is illustrated by eq 16. The *Z*-silyl ether 12 prepared from hexanoic acid through a highly imaginative sequence³⁵ gave the erythro aldol 13 in good yield. Note that there is currently no published method to convert 3-octanone directly to this aldol.

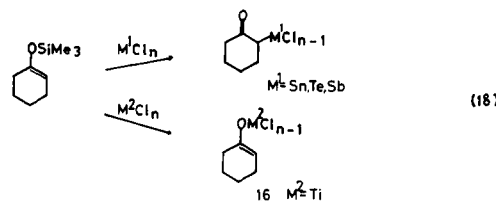


This transmetalation approach allowed, for the first time, the preparation of the tetrasubstituted boron enolates, e.g., 15 from 14, the significance of which will be discussed later.



Subsequent studies concerning the interaction of enol silyl ethers with Lewis acids involved the screening of many metal chlorides in the periodic table, and these studies were stimulated by the impressive versatility of the ring cleavage reaction of 1-alkoxy-1-siloxycyclopropanes (a homologue of enol silyl ether) as a route to metal homoenolates.³⁶

After an extensive investigation, we found that the transmetalation reaction occurs via either an O- or a C-metalation pathway (eq 18), in which SnCl_4 ,³⁷ TeCl_4 , and SbCl_5 ³⁸ took the former pathway and TiCl_4 took the latter.³⁸



The formation of α -metallo ketones, particularly, α -trichlorostannyl ketones, was surprising in two ways:

(34) (a) Inoue, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* 1980, 53, 174 and references therein. (b) Hiram, M.; Garvey, D. S.; Lu, L. D.-L.; Masamune, S. *Tetrahedron Lett.* 1979, 3937. (c) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* 1981, 103, 3099. (d) Reviews: Evans, D. A.; Nelson, J. V.; Taber, T. R. *Topics Stereochem.* 1982, 13, 1. Heathcock, C. H. "Asymmetric Synthesis"; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 2.

(35) Kato, M.; Mori, A.; Oshino, H.; Enda, J.; Kobayashi, K.; Kuwajima, I. *J. Am. Chem. Soc.* 1984, 106, 1773.

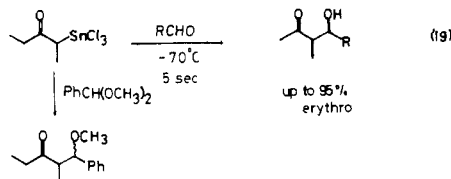
(36) (a) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* 1979, 99, 7360; 1983, 105, 651; 1985, 107, 2138. Nakamura, E.; Shimada, J.-i.; Kuwajima, I. *Organometallics* 1985, 4, 641. (b) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* 1984, 106, 3368. Oshino, H.; Nakamura, E.; Kuwajima, I. *J. Org. Chem.*, submitted for publication.

(37) Nakamura, E.; Kuwajima, I. *Chem. Lett.* 1983, 59.

(38) Nakamura, E.; Shimada, J.-i.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* 1983, 24, 3341.

this result sharply contrasts with the thermodynamic preference for the related enol O-trialkylstannyl ethers, and it was remarkable that SnCl_4 , a typical hard acid, prefers the attachment to the softer part of the enolate structure. The Sn-C bond formation is considered to be a primary process, since the tetrasubstituted enol silyl silyl 14 is inert to SnCl_4 under the conditions where 1 reacts smoothly.

The stannyl ketones undergo aldol addition with high (kinetic) erythro selectivity (eq 19),³⁹ which represents one of the few showpieces that attest the value of α -metallo ketones for organic synthesis.^{16,40} The stannyl ketones react with benzaldehyde acetal, however, in a nonselective manner. α -Telluro and α -stibino ketones were unreactive toward aldehydes.

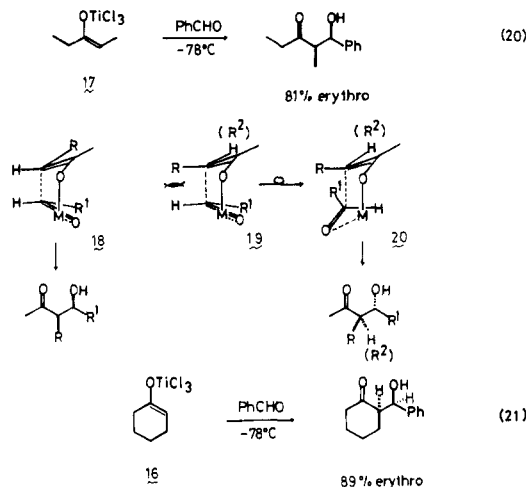


Since relatively little has been known for the transition-metal enolates, we were intrigued by the properties of the trichlorotitanium enolates (eq 18), whose properties resides in the relatively poor electron density of the olefin as indicated by the ¹³C NMR spectra.³⁸ The powerful electron-withdrawing effect of the metal atom almost cancels out the resonance effect of the oxygen atom.

As mentioned earlier in this Account, analysis of the diastereomeric chair TS' has long been the standard protocol in aldol chemistry, and the geometry of the starting enolate regulates the diastereoselectivity of the reaction.^{34d,e} The general validity of this hypothesis, particularly for enolates complexed with Lewis acidic metals (e.g., dialkylboron), appeared unquestionably correct (evidently not so at the present moment). Some early examples of aberrant cases, in which the reaction displays erythro selectivity irrespective of the enolate geometry (so-called "erythro selective aldol reaction"), had been rationalized either by nonchelated open TS's⁴² or by Evans' theorem of a chair/boat interchange of chelated TS's enforced by bulky ligands (e.g., cyclopentadienyl group) on the metal.^{43a} It is interesting to note that these two hypotheses, with rather optional evaluation of the acidity of the metal cation, are, in general, operationally equivalent (cf. ref 43a and 43b).

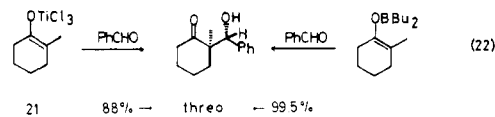
The prominent acidity of the TiCl_3 moiety led us to expect the "usual" course for the reaction via chelated chair TS's. We therefore rather reluctantly tried the reaction, and the *Z*-enolate 17, in an uneventful process, gave an erythro aldol (eq 20). To our surprise, the *E*-enolate 16 also produced an erythro adduct under kinetic control (eq 21), suggesting that the reaction proceeded via some kind of a boat TS.^{41a} The Evans

theorem did not seem to apply, since the chlorine ligands are not very sterically demanding and the geometry of the enolate itself must be regulating the diastereoselectivity. A related case of the trialkoxy- and tris(dialkylamino)titanium enolates also exhibited the same trend in diastereoselection.^{41b}



In a boat TS that forces the *E* enolate to the erythro pathway, we propose the one in which reactants are placed in a tilted position, possibly with some twisting (18).⁴¹ Given the long Ti-O bond length, this TS seems relatively free of strain. The virtue of this boat TS is its concordance to the well-established Burgi-Dunitz trajectory in the nucleophilic attack on a carbonyl group.⁴⁴ When the *Z* enolate enters into a similar reaction, the boat TS 19 is destabilized by the substituent cis to the oxygen, and the conventional chair TS 20 is again favored.

Strong support for this "tilted-boat/chair switching theorem" emerged from studies on the reaction of the enolate 21 derived from 14 (eq 22). For this enolate with an extra methyl group on the olefin, a dramatic reversal of the diastereoselectivity occurred to produce, in ca. 90% selectivity, the threo aldol.⁴⁵ This aldol must have been produced through the conventional chair TS, as the same aldol was formed from the corresponding boron (15) and lithium enolates (eq 22).



This change of the TS is, however, not unreasonable in light of the present proposal. The crucial substituent R (in 19) of the tetrasubstituted enolates (with R^2) experiences severe steric hindrance in the boat TS 19 (just as for *Z* enolates). The R substituent does not experience much steric repulsion in the chair TS 20, because of the absence of any 1,3-diaxial interaction, which is like the conventional cases with *Z* enolates.³⁴ Any hypothesis based solely upon chair TS's fails to rationalize these observations. It is of note that tetra-

(44) Burgi, H. G.; Dunitz, J. D.; Shefter, E. *J. Am. Chem. Soc.* 1973, 95, 5065.

(45) The crystal structure of this threo aldol, which established the stereochemical assignment, also revealed that the compound in a crystalline state, against the well-accepted hypothesis concerning the behavior of aldols in solution,^{34d} is not internally hydrogen bonded but externally bonded to form a dimer: Williard, P. G.; Nakamura, E.; Kuwajima, I. *Acta Crystallogr., Sect. C*, submitted for publication.

(39) Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* 1983, 24, 3347.

(40) Yamamoto, Y.; Maruyama, K. *J. Am. Chem. Soc.* 1982, 104, 2323.

(41) (a) Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* 1983, 24, 3343.

(b) Reetz, M. R.; Peter, R. *Ibid.* 1981, 22, 4691.

(42) (a) Dubois, J. E.; Dubois, M. *J. Chem. Soc., Chem. Commun.* 1968, 1567; *Tetrahedron* 1972, 28, 1665. (b) Kyriakou, G.; Loupy, A.; Seyden-Penne, J. *J. Chem. Res., Miniprint* 1978, 0251. (c) Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* 1980, 102, 3248. (d) Yamamoto, Y.; Yatagai, H.; Naruta, Y.; Maruyama, K. *J. Am. Chem. Soc.* 1980, 102, 7107.

(43) (a) Evans, D. A.; McGee, L. R. *Tetrahedron Lett.* 1980, 21, 3975.

(b) Yamamoto, Y.; Maruyama, K. *Tetrahedron Lett.* 1980, 21, 4607.

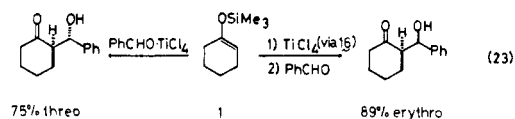
substituted enolates such as 15 should prove to be a good probe for the differentiation between the boat/chair TS's and the open TS's, since the former anticipates threo formation and the latter would generally predict a mixture of stereoisomers.

The role of the boat TS's appears quite general and complementary to the conventional chair TS's with equatorial orientation of substituents. The aldol reaction of the dialkylboron *E* enolates tend to show rather poor threo selectivity (e.g., only 67% threo for 11),³⁴ and the reason of this anomaly has been obscure. We have found that the 2-methyl group on the olefin (i.e., 15) drastically decreases the erythro fraction (99.5% threo, eq 22).⁴¹ This is a good indication that the formation of the erythro product from 11 is due to the boat TS. Similar observations were made for the corresponding lithium enolates.^{41a}

The importance of the boat TS in the analysis of aldol chemistry appears to be increasing: even boron enolates, if the metal bears alkoxy groups in stead of alkyl groups, do not conform to the conventional protocol.⁴⁶ Further studies are definitely needed to trace the factors that control the structure of the TS's.

A corollary to the above studies was that they gave insight into the mechanism of the Mukaiyama aldol reaction,⁴⁷ in that this reaction at low temperatures does not proceed via titanium enolates (eq 23).³⁹ The

diastereoselection under the standard titanium-mediated Mukaiyama conditions is known to conform to the chair TS protocol, while titanium enolates,^{41a} as described above, behave to the contrary.



Concluding Remarks

We have investigated the metathetic generation of reactive enolates, some known and some previously unknown, which are either tightly bound to the counteraction or only very loosely bound. We have often focused on the characterization of the enolate species, in order to make rational use of them in the development of new synthetic reactions. Other workers have also made significant contributions through manipulation of transient metal enolate species.⁴⁸ Further studies on the metathesis involving this fruitful semi-reactive species, the enol silyl ether, will surely contribute still more to ingenious developments in the field of enolate chemistry.

We gratefully acknowledge and sincerely thank our various collaborators whose names appear in the references. We also thank Toray Silicone for continuous supply of some organosilicon compounds throughout the studies.

(46) (a) Hofmann, R. W.; Ditrich, K. *Tetrahedron Lett.* 1984, 25, 1781. Gannari, C.; Cardani, S.; Colombo, L.; Scolastico, C. *Tetrahedron Lett.* 1984, 25, 2283.

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(48) For instance: (a) Ito, Y.; Konoike, T.; Saegusa, T. *J. Am. Chem. Soc.* 1975, 97, 649. Ito, Y.; Aoyama, H.; Saegusa, T. *J. Am. Chem. Soc.* 1980, 102, 4519 and references therein. Kende, A. S.; Roth, B.; Sanfilippo, P. J. *J. Am. Chem. Soc.* 1982, 104, 1784. (b) Inaba, S.; Ojima, I. *Tetrahedron Lett.* 1977, 2009.