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Studies on the Reactive Species in Fluoride-Mediated Carbon−Carbon Bond-Forming Reactions: Carbanion Formation by Desilylation with Fluoride and Enolates

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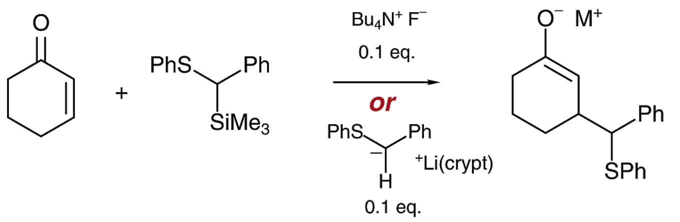

The reactive species in fluoride-mediated carbon−carbon bond-forming reactions was investigated. The regio- and diastereoselectivities of silanes reacting with cyclohexenone in the presence of a catalytic amount of fluoride was compared to the reactivity of analogous solvent-separated lithium ion pairs. Closely analogous behavior was observed, showing that carbanions and not siliconate complexes are the reactive species in the fluoride-catalyzed reactions. Spectroscopic investigations unambiguously show that phenylthiobenzyl anion will form by reaction of silane with tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) or crypt[2.1.1]-solvated lithium enolates. The catalytic cycle runs smoothly with the crypt[2.1.1] complex of α-(phenylthio)benzyllithium as the initiator and enolate as the carrier of the desilylation reaction.

Introduction

In 1978, Hosomi, Shirahata, and Sakurai reported the transfer of an allyl group from allyltrimethylsilane to aldehydes or ketones in the presence of a catalytic amount of fluoride anion to produce homoallylic alcohols or, in the case of α,β-unsaturated carbonyl compounds, 1,4-addition products as well (Figure 1).[1a]

Since then, this type of fluoride catalysis has been extended to the transfer of a variety of moieties, including benzyl,[2a] phenylthiomethyl,[2b] cyclopropenyl,[2c] α-amido- and aminobenzyl,[2d] 1-acyloxy-2-propenyl,[2e] alkynyl,[3a,4] dithianyl,[5] and hydride.[2f,6a] Although the utility of these reactions is considerable, the nature of the reactive species remains elusive. Sakurai and co-workers showed that both α and γ regioisomers were observed when trimethyl(3-methyl-2-butenyl)silane reacted with benzaldehyde,[1a] that crossover products were formed,[1d] and that crotyl and α-methylallyl silanes interconverted with fluoride catalysis.[1d] On the basis of these experimental results, they concluded that

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(1) (a) Hosomi, A.; Shirahata, A.; Sakurai, H. *Tetrahedron Lett.* **1978**, *19*, 3043−3046. (b) Kira, M.; Sato, K.; Sakurai, H. *J. Am. Chem. Soc.* **1988**, *110*, 4599−4602 (c) Sakurai, H. *Synlett* **1989**, *1*, 1−8. (d) Hosomi, A.; Shirahata, A.; Sakurai, H. *Chem. Lett.* **1978**, 901−904.

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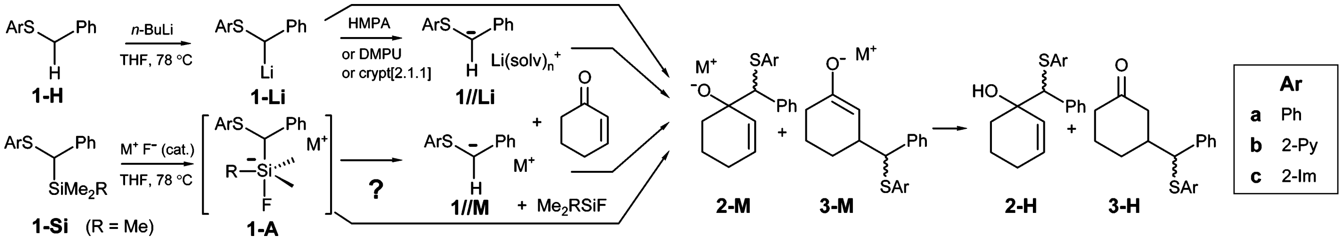
SCHEME 1. Proposed Test for Detection of Siliconate Complex Reactivity



the reactive species was a free carbanion intermediate. On the basis of a high axial selectivity on reaction of a nucleophilic acetylide formed by fluoride-catalyzed desilylation (we will refer to these reactions as fluorodesilylations), Kuwajima, Nakamura, and Hashimoto[3a] also argued that a free acetylide anion was a likely intermediate. Majetich and co-workers showed that the fluoride-catalyzed allyl transfer was, in some cases, superior to other methods, especially for conjugate addition to α,β-unsaturated nitriles and esters. They proposed that it was the intermediate siliconate complex which was the reactive species, largely on the basis of considerations of the high pK_a value of the allyl anion being generated.[7] McDougal and co-workers also proposed a siliconate complex as the reactive nucleophile in a stereospecific fluoride desilylation−benzaldehyde trapping applied to the syn and anti diastereomers of a phenylthioalkylsilane.[8] Hydride transfers from hydrido siliconate complexes seem to be well established.[2f,6a,9]

When the silicon bears multiple electronegative substituents (F, O, N), dissociation of the C−Si bond to form free anion becomes more endothermic. The silicon also becomes more electrophilic, and regiospecific and stereospecific allyl transfer directly from siliconate complex intermediates has been demonstrated in multiple systems[1b,1c,6b,10−12] and has been proposed for alkynyl[13] and other transfers. The question we ask here is whether siliconate complexes bearing only a single electronegative group on silicon are effective nucleophiles.

Although it is possible to make arguments for either mechanism, there has been no systematic study of the catalytic cycle of Figure 1, nor have direct tests to detect the reactivity of intermediate siliconate complexes been reported. In this article, we describe our efforts to address this issue by comparing the diastereo- and regioselectivities of the carbanionic species formed in the fluorodesilylations with that of separated ion pairs (SIPs) formed by treating lithium reagents with the strongly coordinating cosolvents HMPA (*N*,*N*,*N*′,*N*′,*N*″,*N*″-hexamethylphosphoric triamide), DMPU (*N*,*N*′-dimethylpropyleneurea),[14a] and crypt[2.1.1] (4,7,13,18-tetraoxa-1,10-diazabicyclo[8.5.5]-eicosane)[15] as outlined in Scheme 1. We have characterized the solution structure including ion-pair status and reactivity of a number of lithium reagents[16a−c] and have also investigated the reactivity of hypervalent iodine, tellurium, and tin ate complexes in conjunction with some studies on metal−metalloid exchange reactions.[16d] Thus, we felt we were well situated to investigate the reactive species in the desilylation reactions.

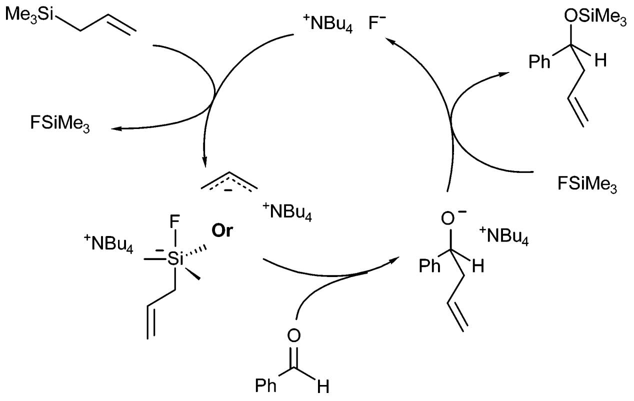


FIGURE 1. Proposed catalytic cycle of fluoride-mediated allylation of benzaldehyde with allyltrimethylsilane.

To effectively make such comparisons, several constraints need to be placed on the carbanionic species. First, the lithium reagent must demonstrably form separated ion pairs upon addition of HMPA or other cosolvents, so that it can be reasonably assumed that the SIP is the reactive species.[16a] Second, the fluoride reaction conditions need to resemble those where the solution structure is known, i.e., low temperature (−78 to −120 °C) in THF or THF/ether solvent. This requirement

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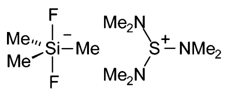
precludes us from examining the original reaction of allyltrimethylsilane, as the fluoride-catalyzed reactions require heating to reflux in THF, where the stability of the SIP is questionable and where HMPA−Li exchange processes are rapid on the NMR time scale, making it difficult to obtain information about ion-pair status by NMR studies.

We chose the α-phenylthiobenzyl moiety (**1a-M**) as the main substrate for our study. Not only has the solution structure of the lithium reagent been thoroughly investigated with a variety of cosolvents,[17] but the selectivity of a close analogue (α-phenylthio-*m*-methylbenzyllithium) in addition to enones has been probed and correlated to the solution structures. The regioselectivity changes from 1,2- to 1,4-addition upon conversion of the contact ion pair (CIP) **1a-Li** to the separated ion pair (SIP) **1a//Li** by addition of HMPA.[16b,18] There are also substantial changes in stereoselectivity.

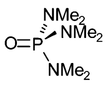
Results and Discussion

If the reactive intermediate in the fluoride desilylation is the free carbanion **1a//M** (Scheme 1), then the regio- and diastereoselectivities of the fluoride-catalyzed reaction should be identical or very similar to those of the solvent-separated lithium reagent **1a//Li** (depending on the identity of M^+). If the active nucleophile is a pentavalent silicon species **1a-A**, the two reactions should display different selectivities.

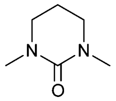
The design of these experiments assumes that the cation, either Bu_4N^+ or solvated Li^+, does not affect the selectivity of these reactions. We were encouraged by the observation[16b] that the *m*-methyl analogue of **1a//Li** gave identical diastereomer ratios (four stereoisomers) upon reaction with 5-trimethylsilyl-2-cyclohexenone whether the counterion was $Li(HMPA)_4^+$, $Li(DMPU)_4^+$, or $Li(crypt)^+$. Nevertheless, it has been well established that chiral ammonium counterions can impart high asymmetric induction in alkylation reactions of enolate ion pairs even if there is no obvious strong interaction between cation and anion (e.g., a hydrogen bond).[19a,19b] However, such reactions are invariably performed in solvents of very low dielectric constant and have only been successful with enolates, where close association (perhaps even hydrogen bonding) between the negative oxygen(s) and positive hydrogens α to the ammonium center is possible, as shown by crystal and solution structures of such ion pairs.[20]



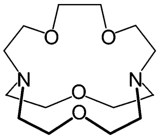
TASF



HMPA



DMPU



crypt[2.1.1]

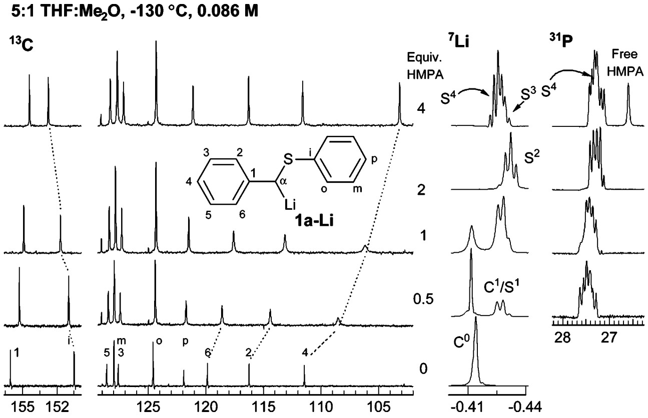


FIGURE 2. HMPA titration of 1a-Li in 5:1 THF/Me_2O, 0.086 M, at ca. −120 °C. ^{13}C, ^7Li, and ^{31}P spectra are shown. The pentet in the ^7Li NMR spectrum at 4 equiv of HMPA indicates full ion-pair separation with four HMPA molecules solvating the lithium cation (C^n and S^n = CIP and SIP bonded to *n* HMPA molecules).

Ideally, we could use the same counterion for both experiments by performing the fluorodesilylation reaction with a solubilized form of LiF, but a number of attempts to execute such reactions failed. Thus, treatment of LiF with excess HMPA [to form $Li(HMPA)_4^+ F^-$] or 12-crown-4 [to form $Li(crown)_2^+ F^-$] did not lead to solutions with catalytic activity with silanes such as **1a-Si**. To avoid the problem that LiF might simply dissolve too slowly to provide useful levels of soluble fluoride, we tested solutions formed by the reaction of *n*-BuLi with Bu_3SiF in the presence of excess HMPA, but such reactions immediately produced a precipitate, assumed to be LiF, and showed no catalytic activity. Reaction of PhLi with Ph_3SiF in THF/HMPA [to presumably form $Ph_4SiF^- Li(HMPA)_4^+$] gave solutions that were also not catalytically active. Examination by ^{13}C NMR spectroscopy showed a 4:3 ratio of Ph_4Si to a compound identified as $Ph_3SiF_2^-Li^+$ from the similarity of its spectrum to that of tetrabutylammonium triphenyldifluorosilicate (TBAT).

In addition to **1a-M**, we examined a number of other nucleophiles, choosing systems where the carbanion carbon bears at least two anion stabilizing groups (vinyl, alkynyl, arylthio, alkylthio), so that the lithium reagents would form separated ion pairs with HMPA. For those systems where a successful alkyl transfer on desilylation could be achieved (**1a-Si, 1b-Si**, **1c-Si**, **4a-Si**, and **4b-Si**), the corresponding lithium reagents were characterized spectroscopically to confirm that complete ion separation occurred.

Structure of the Lithium Reagents. (i) α-Phenylthiobenzyllithium (1a-Li). This lithium reagent has been extensively studied by ^{13}C and ^1H NMR spectroscopy in THF, as well as with various cosolvents.[17] The ^{13}C NMR chemical shifts, particularly those of the para benzyl carbon C-4 and the C−S carbon (C-*i*), are sensitive measures of the level of charge delocalization into the phenyl and benzyl rings and thus of the level of ion separation, with C-4 moving upfield by 8 ppm and C-*i* downfield by 3 ppm upon conversion of the CIP to the SIP. With HMPA as the cosolvent, complete conversion to the separated ion pair **1a//Li** is evident in the ^7Li NMR spectra by the presence of the $Li(HMPA)_4^+$ pentet at low temperature.[16a] Figure 2 shows the ^{13}C, ^7Li, and ^{31}P NMR spectra of **1a-Li** upon treatment with HMPA. As reported previously, the two ortho carbons (C-2 and C-6) are nonequivalent because of slow

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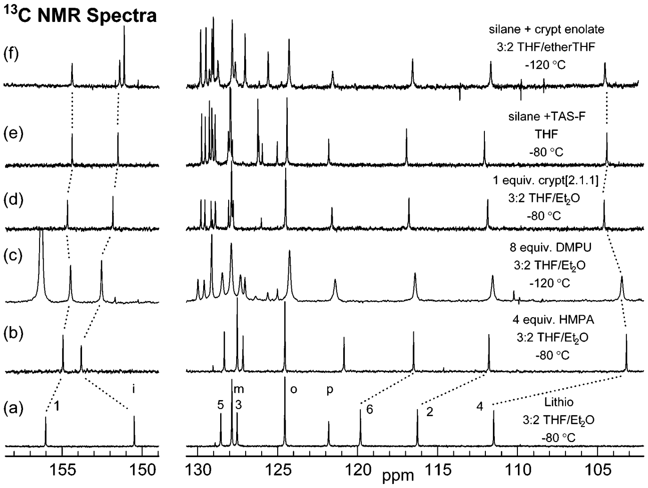

FIGURE 3. ^{13}C NMR spectra of **1a//M** with various counterions, all in 3:2 THF/ether except for e, where solubility of the TASF required pure THF solvent: (a) **1a-Li**; (b−d) SIP **1a//Li** with Li(HMPA)$_4^+$, Li(DMPU)$_n^+$, and Li(crypt)$^+$ as counterions; (e) **1a//(Me$_2$N)$_3$S**$^+$ formed by reaction of **1a-Si** with TASF; (f) **1a//Li**(crypt) formed by reaction of **1a-Si** with crypt-complexed cyclohexanone lithium enolate. The signal at δ 150.1 ppm is the C−OSiMe$_3$ carbon of cyclohexanone enol silyl ether.

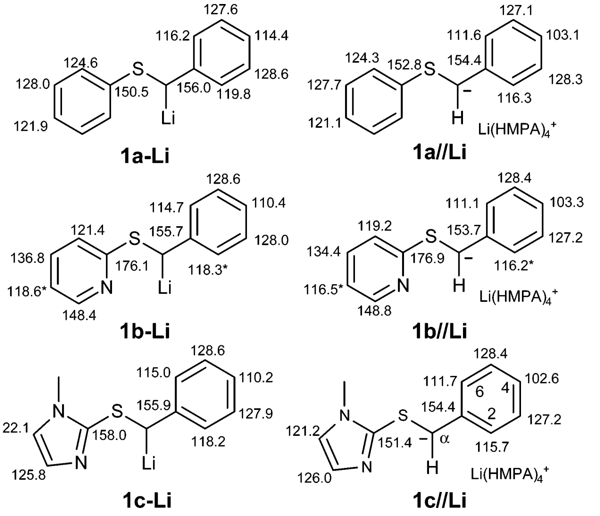

FIGURE 4. ^{13}C chemical shifts of **1b-Li** and **1c-Li** in 3:2 THF/ether at ca. −120 °C with and without HMPA. The carbanion carbon signals were not identified. The assignment for signals marked with an asterisk could be reversed.

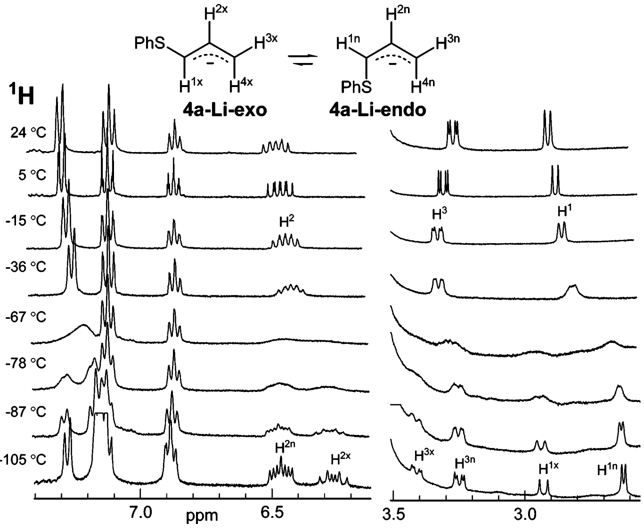

FIGURE 5. Variable-temperature ^{1}H NMR study of **4a-Li** in THF showing coalescence of the endo and exo isomers.

TABLE 1. ^{13}C Chemical Shifts (ppm) of 1c-Li in 3:2 THF/Ether and with Various Cosolvents

additive	C-α	C-1	C-2	C-6	C-4
none	158.0	155.9	118.2	115.0	110.2
DMPU	157.4	155.8	118.0	114.3	108.3
crypt	154.4	150.2	115.9	112.0	104.0
HMPA	154.4	151.4	115.7	111.7	102.6

rotation of the phenyl (coalescence at ca. −10 °C for the CIP, $G^‡ = 14.2$ kcal/mol,[17b] and above 20 °C for the SIP[21]).

Because the impact of the counterion on the reactivity of the carbanion is a key issue in this study, we compared the ^{13}C shifts of **1a//M** with several counterions (Figure 3). The chemical shifts of the SIP with HMPA and DMPU as cosolvents were nearly identical, whereas those with crypt[2.1.1] were significantly different but nearly identical to those formed by reaction of **1a-Si** with tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF), where TAS is the counterion. We rationalize these shift changes qualitatively in terms of the closeness of approach between the carbanion and the centers of positive charge of the cation. For the Li(HMPA)$_4^+$ and Li(DMPU)$_4^+$ species, the lithium cation is significantly more insulated from the anion (closest approach: Li$^+$···OPNCH···C$^-$, Li$^+$···OCNCH···C$^-$) than for the Li(crypt)$^+$ counterion (closest approach: Li$^+$···NCH···C$^-$). The latter shows shifts closer to that of the CIP, indicating a reduced level of negative charge delocalization into the benzyl system (δ of para carbon C-4). Similarly, the trigonal (as opposed to tetrahedral) nature of the (Me$_2$N)$_3$S$^+$ counterion allows a closer approach of anion and cation and a correspondingly smaller chemical shift effect.

(ii) α-(2-Pyridylthio)- and α-[2-(*N*-methylimadazolyl)]-thiobenzyllithium *(1b-Li, 1c-Li).* These lithium reagents were characterized by ^{13}C, ^{7}Li, and ^{31}P NMR spectroscopy in THF solvents at low temperature and were shown to form separated ion pairs upon treatment with ≥4 equiv of HMPA. The chemical shifts are shown in Figure 4. Similarly to **1a-Li**, **1c-Li** showed small differences in the chemical shifts (Table 1), particularly of the sensitive para benzyl carbon C-4, when the counterion was changed, with Li(HMPA)$_4^+$ showing the largest shift effects. The HMPA titration[21] showed the additional interesting effect that a separate set of ^{13}C signals was seen for the mono-HMPA complex of the CIP, whereas for **1a-Li**, the carbanion signals were in rapid equilibrium throughout the titration (Figure 2). This is a consequence of the additional barrier to anion interchange imposed by chelation to the imidazole. DMPU was not a strong enough solvent to fully cause ion-pair separation of **1c-Li** (less than 25% SIP with 8 equiv of DMPU). More difficulty in ion separation is commonly seen with chelated vs unchelated lithium reagents, and DMPU is known to be somewhat less effective than HMPA.[14a,16b]

(iii) 1-Phenylthio- and 1-(2-Pyridylthio)allyllithium (4a-Li, 4b-Li). A previous NMR spectroscopic, cryoscopic, and computational study of **4a-Li** concluded that the compound was monomeric and predominantly or exclusively in the endo

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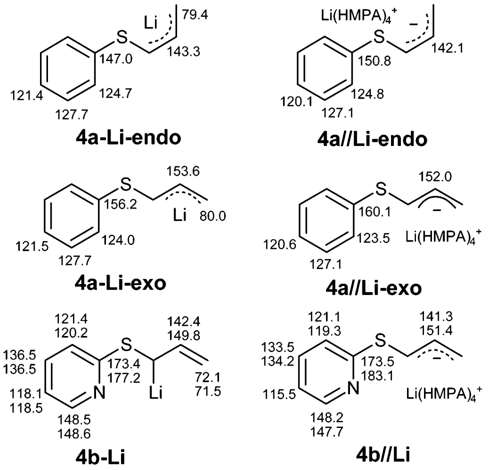
[21] See spectra in the Supporting Information.



^{13}C NMR shifts in 3:2 THF/ether. Upper signal is major isomer (*endo*)

FIGURE 6. ^{13}C NMR data of phenylthio- and pyridylthioallyllithium in 3:2 THF/ether at −120 °C with and without HMPA.

configuration.[22] Computations suggested the endo isomers are more stable than the exo by ca. 6 kcal/mol. These authors examined only the room-temperature ^{13}C NMR spectrum in THF, but report that the ^{1}H NMR spectrum showed no low temperature effects. Our examination of the ^{13}C and ^{1}H NMR spectra of **4a-Li** gave quite different results. At −105 °C, a 2:1 ratio of signals for each proton of the allyl group (Figure 5) is seen, which can be assigned to the endo and exo structures of the CIP on the basis of the coupling of the H-α proton to the central vinyl proton (4.8 Hz for the endo and 11.1 Hz for the exo). The proton (Figure 5) and ^{13}C signals[21] coalesced at ca −50 °C. A similar mixture of isomers was found for the SIP in THF/HMPA. At room temperature, the endo and exo isomers are in dynamic equilibrium, and the reported shifts[22] are consistent with such averaging.

The almost 10 ppm downfield shifts from endo to exo in C-β of the allyl fragment (from 143.3 to 153.6 ppm) and in the phenyl C−S carbon (from 150.8 to 160.1 ppm, Figure 6) imply significantly different structures for the two isomers. Earlier workers unfortunately did not calculate the ^{13}C shifts of the exo isomers to provide some insight into these unusual effects.

α-Pyridylthioallyllithium (**4b-Li**) was also present as a mixture of endo and exo isomers in both the CIP (3:2 ratio) and the SIP (3:1) ratio. In each case, the major isomer has the same chemical shift features as the endo isomer of **4a-Li**.

Structure of the Enolate. As discussed below, the enolate intermediate **3-M** of the 1,4-addition reaction plays an important role in the catalytic cycle of the fluorodesilylation reaction. For this reason, we performed experiments to establish the structure of the enolate under the conditions of the experiments. Because **3a-M** is a diastereomeric mixture and has a set of peaks in the aryl region of the ^{13}C NMR spectrum that could overlap with other peaks of interest, we used the enolate of cyclohexanone as a simpler model. The ^{13}C NMR spectra in THF and DME solution have been reported.[23] We confirmed the ^{13}C NMR shifts at δ 159.6 and 89.6 ppm for the vinyl carbons.

The presumptive structure in THF for an unhindered ketone lithium enolate without anion-stabilizing substituents at the α-carbon is a cubic tetramer.[14b,24] Spectroscopic examination, including an HMPA titration,[16a] of the lithium enolate of cyclohexanone in 3:2 THF/ether provided strong evidence for a tetrameric structure both in THF/ether mixtures and with excess HMPA present.[16e]

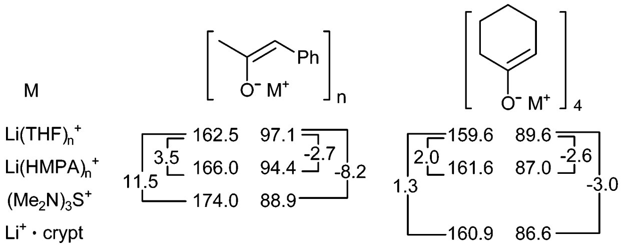


FIGURE 7. Comparison of the vinyl ^{13}C chemical shifts of the known naked TAS enolate of phenylacetone[30] and cyclohexanone lithium enolate with HMPA and crypt[2.1.1].

The structure of cyclohexanone lithium enolate complexed with crypt[2.1.1] is more ambiguous. Addition of excess crypt gave a new major species with significant shifts of the vinyl carbons from δ 159.6 to 160.9 ppm and from δ 89.6 to 86.6 ppm. At least one additional minor species was present. The lithium NMR spectrum also shows several signals. It is unlikely that the species seen is a separated or "naked" crypt enolate, because the chemical shifts did not differ significantly from the HMPA-solvated tetramer signals at δ 161.6 and 87.0 ppm. The lithium enolate of phenylacetone shows chemical shift effects upon addition of HMPA similar to those shown by cyclohexanone, but a much larger effect upon conversion to the naked TAS enolate than cyclohexanone enolate shows upon conversion to the crypt complex (Figure 7). Because the enolate of phenylacetone is probably dimeric in THF[25] and that of cyclohexanone is tetrameric, an authentic monomeric Li(crypt) naked enolate of cyclohexanone should show an even more pronounced shift change than phenylacetone. Perhaps the crypt solvates one of the lithiums in the tetramer to make one or more reactive species of the triple-ion type [e.g., $(RO)_4Li_3^-$ Li(crypt)$^+$].[16c,26,27] We were unable to prepare solutions of the TAS enolate of cyclohexanone for proper chemical shift comparison (reaction of enol silyl ether with TASF gave a precipitate).

Reactivity Studies. (i) Benzyl Sulfides. The selectivity of the lithium reagent **1a-Li** upon reaction with cyclohexenone (Table 2) parallels that of the *m*-methyl analogue previously reported.[16b] In THF, a 36:64 ratio of the 1,2- to 1,4-addition products (**2a-H**, **3a-H**) was formed. The 1,2-product is believed to form by reaction of the CIP, and the 1,4-product from the small amount of SIP present. On addition of excess HMPA, the regioisomer ratio was <0.5:99.5, and there was a substantial change in diastereoselectivity of the 1,4-adduct (from 51:49 to 24:76 dr), attributed to a change in mechanism from a lithium-catalyzed reaction of the separated ion **1a//Li** to one where catalysis has been suppressed by coordination of HMPA to lithium.[16b] Formation of **1a//Li** by addition of crypt[2.1.1] gave the same regio- and stereoselectivities as with HMPA, but

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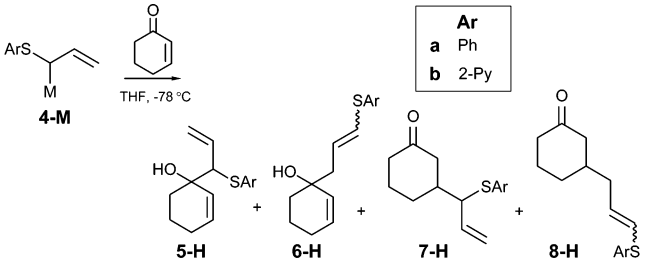
TABLE 2. Comparison of Lithium Reagent and Fluoride Desilylation Regio- and Stereoselectivities in THF at −78 °C (Scheme 1)

nucleophile (R)	conditions	1,2/1,4	1,4 dr	yield[a]
1a-Li	0 equiv of HMPA	36:64	51:49	90
1a-Li	4 equiv of HMPA	<1:99	24:76	90
1a-Li	8 equiv of DMPU	<1:99	35:65	89
1a-Li	1 equiv of crypt	<1:99	25:75	100
1a-Si (Me)	0.1 equiv of TBAF	<1:99	23:77	61 (96)[a]
1a-Si (Me)	0.05 equiv of TASF	<1:99	34:66	87
1a-Si (^{i}Pr)	0.1 equiv of TBAF	<1:99	22:78	73 (92)[a]
1a-Si (Ph)	0.1 equiv of TBAF	<1:99	22:78	30 (87)[a]
1b-Li	0 equiv of HMPA	24:76	47:53	83
1b-Li	4 equiv of HMPA	<2:98	26:74	83
1b-Si (Me)	0.1 equiv of TBAF	<2:98	27:73	36 (71)[a]
1c-Li	0 equiv of HMPA	62:38	51:49	82
1c-Li	4 equiv of HMPA	<3:97	75:25	100
1c-Li	10 eq HMPA	<3:97	76:24	100
1c-Li	8 equiv of DMPU	<3:97	70:30	49
1c-Li	1 equiv of crypt	<3:97	54:46	87
1c-Si (Me)	0.1 equiv of TBAF	<3:97	66:34	81
1c-Si (Ph)	0.1 equiv of TBAF	<3:97	66:34	76
1c-Li	**1c-Li**(crypt)[b]	<3:97	54:46	100

[a] For the fluoride reactions, there was often considerable protodesilylation. The number in parentheses is the total recovery. [b] Using the crypt-separated anion **1c//Li**(crypt) as the promoter of the reaction, as in Scheme 5, instead of a fluoride source.



Ar = Phenyl (**4a-M**)

	5-H	6-H	7-H	8-H
0 HMPA (M=Li)	63% (1:1 dr)	27% (55:45 E/Z)	9%	1%
4 eq. HMPA (M=Li)	<2%	<2%	96% (dr 39/61)	4% (E/Z 3:1)
TBAF (M=SiMe$_3$)	<2%	<2%	96% (dr 39/61)	4%

Ar = 2-Pyridyl (**4b-M**)

	5-H	6-H	7-H	8-H
0 HMPA (M=Li)	12% (1:2 dr)	88% (1:1 E/Z)	<3%	<5%
4 eq. HMPA (M=Li)	<3%	<3%	>95% (dr 41/59)	<5%
TBAF (M=SiMe$_3$)	<3%	<3%	>95% (dr 35/65)	<5%

FIGURE 8. Product ratios from the reaction of arylthioallylmetal reagents **4a-M** and **4b-M**.

addition of DMPU gave a different diastereomer ratio (35:65 vs 24:76). These experiments gave diastereomer ratios reproducible to ±2%, so counterion effects are significant.

The tetrabutylammonium fluoride- (TBAF-) promoted reaction also gave entirely 1,4-adduct with the same diastereomer ratio within experimental error as seen with **1a//Li** formed with HMPA or crypt[2.1.1]. This supports the idea that the separated ion pair is the reactive intermediate in this fluoride-catalyzed reaction. However, a similar TASF-catalyzed reaction gave a slightly different ratio of diastereomers (34:66 instead of 23:77), which, as in the case of the **1a//Li(**HMPA) and **1a-Li**(DMPU) reactions, must then be a consequence of the different counterions in the two reactions [Bu_4N^+ versus $(Me_2N)_3S^+$].

If a pentavalent, negatively charged silicon species (**1a-A**) were the active nucleophile, varying the substituents on silicon would change the reactive intermediate and should result in different product ratios. Changing the silicon group in **1a-Si** from trimethylsilyl to isopropyldimethylsilyl and phenyldimethylsilyl had no effect on the regio- or diastereoselectivities in reactions with 2-cyclohexenone, which lends support to the proposal that **1a-A** is not the active nucleophile in these reactions.

As with the benzyl phenyl sulfide reagents, the contact ion pairs of the pyridyl and *N*-methylimidazolyl analogues **1b-Li** and **1c-Li** gave a different mixture of 1,2- and 1,4-adducts (24:76 and 38:62) upon reaction with 2-cyclohexenone than did the HMPA SIP or fluorodesilylation reaction, which both gave exclusively the 1,4-addition product. However, whereas **1b-M** gave identical diastereomer ratios for both processes, **1c-M** gave small but significant differences as the counterion was changed. The fluorodesilylation gave diastereomer ratios identical to those of the crypt lithium solvate (66:34), but different from those observed for the HMPA- (75:25) and DMPU- (70:30) solvated lithium reagents.

We investigated several hypotheses on these changes in diastereoselectivity. The HMPA-solvated **1c//Li** reaction gave the same diastereoselectivity independent of the amount of HMPA used, and the same selectivity was observed whether a 10-fold excess of **1c//Li** over cyclohexanone or cyclohexanone over **1c//Li** was used. These results tend to rule out contributions from CIP reactions or product-induced structural changes in the active reagents. Altering the silane from trimethylsilyl to phenyldimethylsilyl did not change the diastereomer ratio of 66:34 in the fluorodesilylation reaction. We conclude that, for this system, all reactions are going through the separated carbanion, but the diastereomer ratio is sensitive to the nature of the counterion, perhaps as a consequence of the strong dipole and coordinating ability of the imidazole substituent.

(ii) Allyl Sulfides. We tested the allyl and propargyl systems because they have an additional element of selectivity, the α/γ ratio on the nucleophile, as a probe for changes in reactive intermediate. A siliconate complex mechanism should be more plausible with allyl and propargyl systems because electrophilic attack can occur remote from the point of bonding to the silicon of the siliconate complex rather than at the Si−C bond, as required for the benzyl systems. The behavior of the allyl sulfides **4a-M** and **4b-M** paralleled that of the benzyl systems. The CIP lithium reagents gave >90% 1,2-addition, with quite variable α/γ ratios, favoring α for **4a-Li** and γ for **4b-Li**. These differences are a consequence of the structural changes caused by chelation in **4b-Li**.

The SIP and fluorodesilylation reactions gave no detectable 1,2-addition and each gave >95% α-addition on the allyl fragment (Figure 8).[28] As has been seen for several of the previous systems, there was a small difference in the diastereomer ratio of the α-isomer for **4b-Si**. The diastereoselectivities of the 1,4-adduct were identical for the two reactions for **4a-M**, but for **4b-M**, there was a difference outside our experimental error. As outlined above, these allyl anions have the additional complication that a mixture of exo and endo is isomers present, and this ratio is not necessarily the same for both reactions. Because it is probable that the reactions with cyclohexenone are faster than exo/endo interconversion, this could be a potential source of different diastereoselectivities.

We attempted to study several other systems where regioselectivity in the anion could be used as a probe but where exo/

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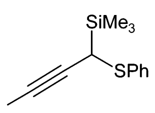
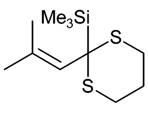
[28] Conjugate additions of metalated allyl sulfides with 1,4-α selectivity have been reported: Binns, M. R.; Haynes, R. K. *J. Org. Chem.* **1981**, *46*, 3790−3795.

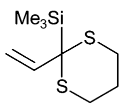
endo isomerism was not an issue. These included propargyl systems such as **9-Si**, allyl systems symmetrically substituted at the termini (**10-Si**, **11-Si**), or allyl systems where the isomer ratio should more strongly favor the endo form (**12-Si**). Each of these should yield carbanions comparable in stability to the successful systems discussed above, but in our hands, the reactions were quite capricious. Treatment of these trimethylsilanes and others like them with TBAF in THF at −78 °C in the presence of 2-cyclohexenone or benzaldehyde gave no addition products: either starting silane was recovered or protodesilylation reactions were observed when more forceful conditions were employed. The reasons are still poorly understood, but steric hindrance appears to be a factor. For example, the structure of **12-Si** differs from that of **4a-Si** by only a methyl group β to the carbanion, and several others have a higher level of substitution at the reacting centers. However, steric effects cannot be used to explain the failure of the propargyl system **9-Si** to react, whereas the allyl analogue **4a-Si** undergoes facile addition to 2-cyclohexenone in the presence of TBAF.



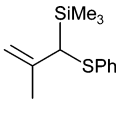
9-Si



10-Si



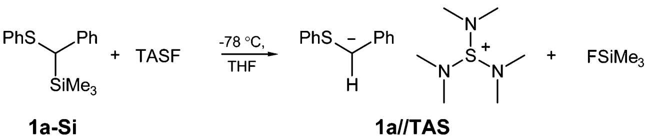
11-Si



12-Si

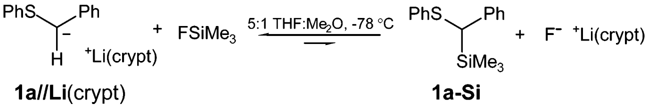
Catalytic Cycle. We investigated each step in Sakurai's proposed catalytic cycle (Figure 1) using low-temperature ^{13}C, ^{7}Li, ^{19}F, and occasionally ^{29}Si NMR spectroscopy, in the hopes of directly observing either the pentavalent siliconate or the separated ion pair. Reaction of a stoichiometric amount of TBAF dried over 4-Å molecular sieves with the silane **1a-Si** resulted in protodesilylation, presumably because of water or HF_2^- in the fluoride solution.[29] The more anhydrous TBAT[5] was unreactive with **1a-Si** at −78 °C. Fortunately, TASF proved to be an effective anhydrous fluoride source, although it was only partially soluble in THF. Upon reaction with 1 equiv of **1a-Si** in THF at −80 °C, a new species was visible in the ^{13}C NMR spectrum (Figure 3e) that closely matched the spectrum of the crypt-separated ion (Figure 3d), indicating that the carbanion was generated under these conditions. A small amount of protodesilylated phenyl benzyl sulfide was also observed (Scheme 2).

SCHEME 2



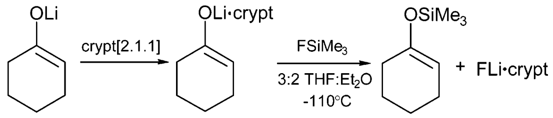
Approaching this equilibrium from the other side, trimethylsilyl fluoride was added to crypt-solvated carbanion, **1a//Li**(crypt). The aryl peaks corresponding to the separated anion did not change, and no signals corresponding to **1a-Si** could be detected (Scheme 3). The doublet of trimethylsilyl fluoride was visible in the ^{13}C NMR spectrum at δ −0.26 ppm with $^{2}J_{C-F} =$ 15.1 Hz. Thus, the equilibrium does not favor silylation at carbon with trimethylsilyl fluoride even when highly stable LiF could be formed. A minor amount of protonation product **1a-H** was observed from small amounts of protic impurities (HF, H_2O) in the trimethylsilyl fluoride. An alternative route to **1a-H**, protonation of **1a//Li** by **1a-Si** to form $PhS(SiMe_3)PhCLi$, does occur after extended reaction times at higher temperatures (−50 °C for 2 h), but was not a significant problem in short-term experiments at −78 °C.

SCHEME 3



The next proposed step in the catalytic cycle is the reaction of the enolate **3a-M** with trimethylsilyl fluoride to regenerate fluoride ion. To reduce spectral interference in the ^{13}C NMR studies, we used the crypt lithium enolate of cyclohexanone as a model. Upon addition of trimethylsilyl fluoride, the ^{13}C NMR peaks for the lithium enolate disappeared, and peaks corresponding to the trimethylsilyl enol ether appeared. Thus, trimethylsilyl enol ether formation is favored from the reaction of crypt-solvated lithium enolate with trimethylsilyl fluoride. This is interesting considering the observations of Noyori and co-workers, who formed the tris(diethylamino)sulfonium enolate of phenylacetone by cleavage of the corresponding trimethylsilyl enol ether with TASF with the concomitant formation of trimethylsilyl fluoride.[30] Our system differs from theirs in the substantially higher pK_a of the ketone (26.4 vs 18.7 in DMSO[32a]) and in the presence of lithium cation. A precipitate that forms during the reaction, presumably lithium fluoride, might be displacing the equilibrium toward enol silyl ether formation (Scheme 4).

SCHEME 4



The reactive nature of the crypt enolate with trimethylsilyl fluoride suggested that the enolate should also be competent in the desilylation of **1a-Si** (an oxydesilylation). Accordingly, cyclohexanone enolate was generated in 3:2 THF/ether solution and solvated with 1.8 equiv. of crypt[2.1.1]. Upon addition of **1a-Si**, the solution turned bright yellow, and peaks corresponding to cyclohexanone enol trimethylsilyl ether appeared at δ 151.0, 102.6, and 0.1 ppm. Two additional new species were present in a 2:1 ratio: the crypt-separated ion pair **1a//Li**(crypt) (Figure 3f) and the protodesilylation product **1a-H**. Upon quenching with trimethylsilyl chloride, the peaks of the crypt SIP disappeared, and silane **1a-Si** was observed. In contrast, the HMPA-solvated lithium enolate does not react with the silane **1a-Si**.

The formation of the α-(phenylthio)benzyl carbanion from silane **1a-Si** using solvated enolate implies that the tetrabutylammonium enolate could be the actual chain carrier in these fluorodesilylation reactions, with fluoride functioning only as an initiator. To test this possibility, we performed experiments with a catalytic amount of enolate replacing the fluoride salt, using the crypt-solvated lithium enolate as a model of the tetrabutylammonium enolate. A catalytic amount (0.1 equiv) of **1a//Li**(crypt) was prepared, and full equivalents of the silane

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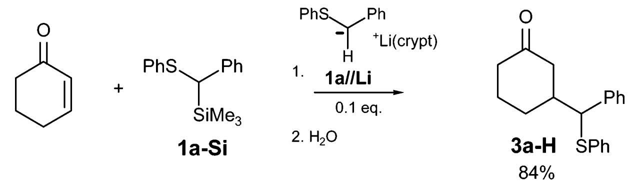
[29] We found that drying a 1 M THF solution of $Bu_4N^+F^-$ with 4-Å molecular sieves[1a] produced the most effective fluoride source for these reactions. Drying under high vacuum with warming[31a] or reaction of $Bu_4N^+CN^{-}$[31b] with hexafluorobenzene did not give useful reagents in our hands.

1a-Si and 2-cyclohexenone were added to the solution at −78 °C (Scheme 5). No source of fluoride ion was included. To realize more than a 10% conversion to products, the enolate intermediate **3-Li**(crypt) formed by reaction of the carbanion initiator with 2-cyclohexenone must actively regenerate the carbanion from the silane **1a-Si**. This reaction yielded 84% 1,4-adducts **3-H** and 13% protodesilylated **1a-H**. HMPA-solvated **1a//Li** was not an effective catalyst for this reaction.

SCHEME 5



It is plausible that the enolate catalytic cycle involves the monomeric SIP enolate rather than the aggregated form present at equilibrium, given that the enolate must initially be formed as a separated ion pair by addition of the SIP **1a//Li**(crypt) to cyclohexenone. To form the aggregate, the lithium cation must be extracted from crypt[2.1.1], and this process is known to be quite slow.[33]

A similar reaction using **1c-Si** and a catalytic amount of **1c//Li**(crypt) was also successful. It is significant that the diastereoselectivity of this catalytic reaction was different from that seen for the TBAF-catalyzed reaction of **1c-Si** and for the stoichiometric reactions of **1c//Li**(HMPA) and **1c//Li**(DMPU) but identical to that observed for the reaction of **1c//Li**(crypt) with cyclohexenone.

Thus, a second simpler catalytic cycle that bypasses the regeneration of fluoride ion is operative in these reactions (Figure 9). It is not known whether a typical fluorodesilylation employs the fluoride cycle (right of Figure 9) to carry the reaction or only initiates the process after which the enolate-based one (left of Figure 9) performs the bulk of the reaction. It has been well established that various oxygen nucleophiles can cleave C−Si bonds to form carbanionic species, both intermolecularly[2b,3a,4,13] and intramolecularly, as in various Brook and homo-Brook rearrangements.[3b,16f,19c,34]

Summary. A series of stabilized lithium carbanions (**1a-Li**, **1b-Li**, **1c-Li**, **4a-Li**, and **4b-Li**) was characterized spectroscopically. Each was present as a CIP in THF/ether solvent mixtures and formed separated ion pairs when excess HMPA, DMPU, and/or crypt[2.1.1] was added. The allyllithium reagents **4a-Li** and **4b-Li** were both present as mixtures of endo and exo isomers. The regio- and stereoselectivities of these CIPs and SIPs toward cyclohexenone was compared to that obtained during the fluoride-catalyzed desilylation of the corresponding triorganosilanes. In all cases, the selectivity was very different for the lithium CIP and SIP reactions. However, the regioselectivity in electrophile (exclusive 1,4-addition) and nucleophile (>95% α-addition for the allyl anions) was the same for both the SIP and the fluoride-catalyzed reactions. The diastereoselectivity of the 1,4-adducts was similar, but showed small variations that could be attributed to counterion effects [the counterions used were Li(HMPA)$_4^+$, Li(DMPU)$_n^+$, Bu$_4$N$^+$, and (Me$_2$N)$_3$S$^+$]. Varying the counterions also caused small changes in the ^{13}C NMR spectra of the SIPs. We conclude that an ion-paired carbanion **1a//M** and not a siliconate complex (e.g., **1a-A**) is the reactive species in the fluorodesilylation reactions we have studied, supported by the observation that, in several cases (**1a-Si**, **1c-Si**), no change in selectivity could be detected when the silyl group was altered. Our study provides no direct information on the mechanism of the reactions of allyltrimethylsilane. The likelihood of a switch to a mechanism in which the siliconate complex is a nucleophile should increase as the pK_a of the carbanion conjugate acid increases (the pK_a of **1a-H** in DMSO is 30.8;[32b] that of propene is ca. 44[32c]) and should be more plausible with a delocalized system where electrophilic attack can occur remote from the point of bonding to the silicon of the siliconate complex rather than at the Si−C bond.

The catalytic cycle for **1a-M** was investigated using low-temperature multinuclear NMR spectroscopy. The equilibrium between carbanion/fluorotrimethylsilane and silane/fluoride ion (Scheme 3) was in favor of the former for both (Me$_2$N)$_3$S$^+$ and Li(crypt)$^+$ counterions, so the crucial fluoride ion desilylation to form carbanion is not just kinetically but also thermodynamically favorable. More surprising is the observation that the crypt-solvated lithium enolate of cyclohexanone also performs an exothermic desilylation of **1a-Si** to form **1a//Li**(crypt). This implies that a catalytic cycle in which enolate rather than fluoride is a carrier occurs in these reactions (Figure 9), and such a catalytic process was demonstrated (Scheme 5).

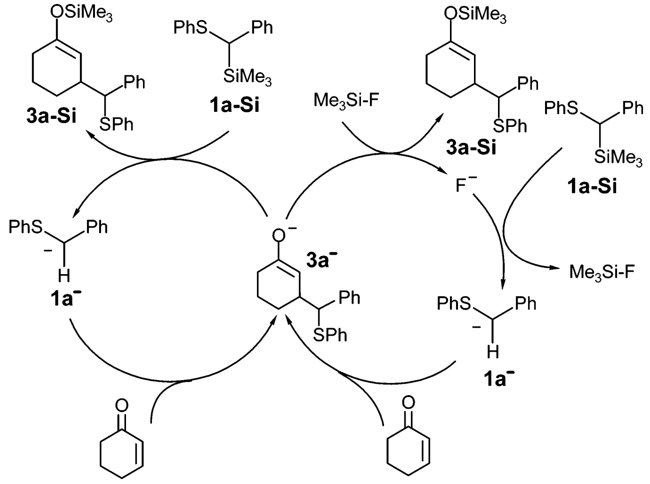


FIGURE 9. Catalytic cycles for fluorodesilylation can be carried out by fluoride and/or enolate. All anions have Bu$_4$N$^+$ as cation.

Experimental Section

Low-Temperature Multinuclear NMR Spectroscopy. Low-temperature NMR experiments were performed on a 360-MHz spectrometer with a 10- or 5-mm broadband probe at the following frequencies: 90.556 MHz (^{13}C), 139.905 MHz (^{7}Li), 145.785 MHz (^{31}P), 338.827 MHz (^{19}F). Spectra were obtained in undeuterated THF, ether, or dimethyl ether or a combination thereof with the spectrometer unlocked. These solvent combinations allowed for the

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cooling of samples to −155 °C without freezing. ^{13}C spectra were acquired with composite pulse decoupling and referenced internally to the C-2 carbon of THF (δ 67.96 ppm). Lorenzian multiplication (LB) was applied to ^{13}C spectra. ^{7}Li spectra were referenced externally to 0.3 M LiCl/MeOH standard (δ 0.00 ppm). ^{31}P spectra were referenced externally to 1.0 M PPh_3/THF standard (δ −6.00 ppm) or internally to free HMPA (δ −26.40 ppm). Gaussian multiplication was applied to ^{7}Li and ^{31}P spectra.

Samples were prepared in thin-walled 10-mm NMR tubes that were stored overnight under vacuum, fitted with 9-mm septa, wrapped with Parafilm, and purged with N_2. Silicon grease was applied to the top of the septum to seal needle punctures. Samples were prepared and stored at −78 °C. For HMPA titrations, spectra of the active nuclei (^{13}C, ^{7}Li) were obtained at temperatures less than or equal to −120 °C. The sample was removed and cooled at −78 °C; the grease from the septum was removed; the desired amount of HMPA was added; the septum was regreased; the sample was reinserted into the probe; the temperature was allowed to equilibrate; and ^{13}C, ^{7}Li, and ^{31}P spectra were obtained. For variable-temperature experiments, temperature equilibration for 5−10 min was allowed before spectra were obtained. Temperature was measured by console reading or by use of tris(trimethylsilyl)methane as an internal thermometer.[16g]

General Lithium Reagent Reaction. Benzyl phenyl sulfide (30 mg, 0.15 mmol) was added to a 5-mL long-neck round-bottom flask, which was then purged with nitrogen, and 2 mL of THF was added. This solution was cooled to −78 °C and metalated with *n*-BuLi (60 μL, 2.58 M). HMPA (104 μL, 0.6 mmol) was added (similarly for DMPU and crypt[2.1.1]), giving an orange solution. 2-Cyclohexenone (15 μL, 0.15 mmol) was added to the solution and allowed to react for several minutes; it was then quenched with 300 μL of a 3 M solution of propionic acid in ether and taken up in 20 mL of 1:1 hexanes/ether. It was then washed once with 15 mL of $NaHCO_3$, twice with 15 mL of H_2O, and once with 15 mL of brine; dried over $MgSO_4$; filtered; and rotary evaporated. Pentachloroethane (9 μL, 0.075 mmol) was added, and the oil was taken up in $CDCl_3$ for ^{1}H NMR analysis to afford 99% recovery, of which 4% was benzyl phenyl sulfide characterized by a singlet at δ 4.13 ppm; 18% was 1,4-regioisomer diastereomer A, characterized by a doublet at δ 4.09 ppm; and 77% was the other 1,4-regioisomer, diastereomer B, characterized by a doublet at δ 4.06 ppm.

General Fluoride-catalyzed Reactions. 1a-Si (68 mg, 0.25 mmol) was added to a 5-mL long-neck round-bottom flask and purged with nitrogen, after which 2-cyclohexenone (24 μL, 0.25 mmol) and 3 mL of THF were added. The solution was cooled to −78 °C, and TBAF (25 μL, 0.025 mmol, 1 M solution made from solid TBAF hydrate dried over 4-Å molecular sieves for 5−10 min prior to use) was added. The solution was allowed to react for 30 min at −78 °C, then quenched with propionic acid in ether (300 μL, 3 M), and allowed to stir for 15 min to cleave enol silyl ethers. The solution was taken up in 20 mL of 1:1 hexanes/ether; washed once with 15 mL of $NaHCO_3$, twice with 15 mL of H_2O, and once with 15 mL of brine; dried over $MgSO_4$; filtered; and rotary evaporated. Pentachloroethane (15 μL, 0.125 mmol) was added, and the oil was taken up in $CDCl_3$ for ^{1}H NMR analysis to afford 96% recovery, of which 35% was benzyl phenyl sulfide, characterized by a singlet at δ 4.12 ppm; 14% was diastereomer A of **3a−H**, characterized by a doublet at δ 4.08 ppm; and 47% was diastereomer B of **3a−H**, characterized by a doublet at δ 4.05 ppm. The diastereomer ratio was confirmed by a GC trace at a flow rate of 3.0 mL/min, with an initial temperature of 100 °C for 4 min, an increase in temperature to 175 °C over 4 min, and finally an increase in temperature to 250 °C over 4 min. The diastereomers appeared at 25.17 and 25.30 min in a 23:77 ratio.

Catalytic Cycle with Crypt[2.1.1]. Benzyl phenyl sulfide (15 mg, 0.075 mmol) was added to a 25-mL round-bottom flask flask, and the flask was purged with nitrogen. To this flask was added 8 mL of THF, and the mixture was cooled to −78 °C. This was metalated with *n*-BuLi (30 μL, 2.58 M, 0.077 mmol), after which the solution turned yellow, and crypt[2.1.1] (20 μL, 0.076 mmol) was added (solution turned bright yellow, almost orange). **1a-Si** (204 mg, 0.75 mmol) and 2-cyclohexenone (73 μL, 0.75 mmol) were added to the solution and allowed to react for 60 min at −78 °C. The solution was quenched with propionic acid in ether (600 μL, 3 M); taken up in 60 mL of 1:1 hexanes/ether; washed once with 40 mL of $NaHCO_3$, once with 40 mL of H_2O, and once with 40 mL of brine; dried over $MgSO_4$; and rotary evaporated. Pentachloroethane (9 μL, 0.075 mmol) was added as an internal standard, and product ratios were determined by ^{1}H NMR spectroscopy.

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Supporting Information Available: Preparation and spectral characterization of starting sulfides (**1-H**, **4-H**), silanes (**1-Si**, **4-Si**, **9-Si**, **10-Si**, **11-Si**, **12-Si**), and products (**2-H**, **3-H**, **5-H**, **6-H**, **7-H**, **8-H**). Experimental details and ^{13}C, ^{7}Li, and ^{31}P NMR spectra of the solution NMR studies of **1a-Li**, **1b-Li**, **1c-Li**, **4a-Li**, and **4b-Li**. Experimental details and spectra of the catalytic cycle studies. Copies of ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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