

Ylides by the Desilylation of α -Silyl Onium Salts

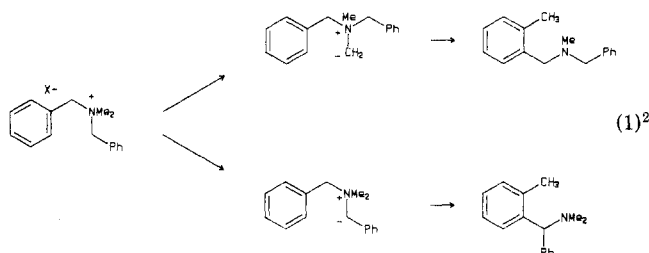
EDWIN VEDEJS* and FREDERICK G. WEST

S. M. McElvain Laboratory of Organic Chemistry, Chemistry Department, University of Wisconsin, Madison, Wisconsin 53706

Received February 19, 1986 (Revised Manuscript Received May 12, 1986)

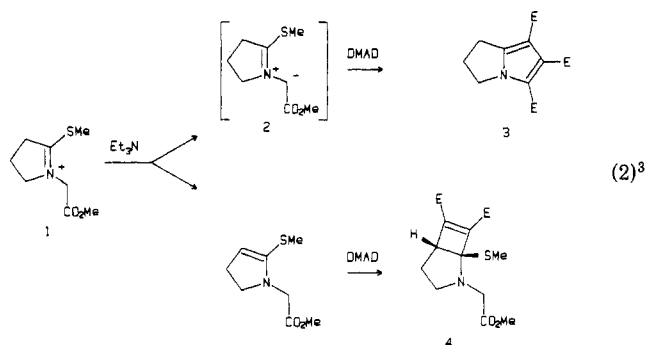
Conventional ammonium, phosphonium, and sulfonium ylides are usually generated from the corresponding "onium" salt by deprotonation with strong base. No other method is necessary if the starting salts have only one available site for α -proton removal and if the resulting ylides are relatively stable. These conditions are met for typical Wittig reagents ($RCH_2P^+R_3 \rightarrow RCH=PPh_3$), and intermolecular ylide reactions are easily performed by adding a carbonyl substrate after the base used for deprotonation is consumed.

Matters are not always so simple with the relatively short-lived ammonium or sulfonium ylides. Some cases require in situ trapping due to ylide decomposition, and intermolecular reactions are best performed with those carbonyl substrates which can tolerate the base used for onium salt deprotonation.¹ Regiochemical problems can also be encountered because more than one type of α -proton may be available kinetically. The Sommelet-Hauser rearrangement of benzyltrimethylammonium salts can usually be controlled to give products derived from kinetically favored methyllide formation. However, there are examples where the thermodynamically favored benzylide is formed depending on the base, resulting in mixtures of rearrangement products (eq 1).²

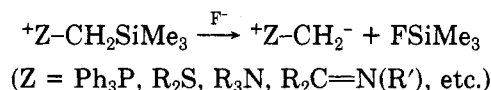


Complications with the deprotonation method can become extreme in cases where the ylide is disfavored by both thermodynamic and kinetic factors. This situation is often encountered with ylides of the 1,3-dipole variety. Thus, attempts to convert thioimidate salt 1 into the azomethine ylide 2 by deprotonation with triethylamine do afford some of the desired pyrrole 3 via [2 + 3] cycloaddition with acetylenedicarboxylate (DMAD). However, the major product is the enamine adduct 4. Stronger bases fail, in part, because they destroy the dipolarophile.³

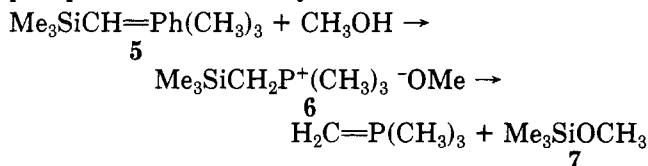
Difficulties of this sort prompted experiments in our laboratory to develop alternatives to the deprotonation method for making ylides. The goals were to (1) control the regiochemistry of ylide formation, and (2) permit in situ trapping of unstable ylides by sensitive substrates. Desilylation of α -trimethylsilyl onium salts by



fluoride is the technique which evolved from these studies:⁴



By way of precedent, ylide mechanisms had been invoked to explain several examples of nucleophile-induced decomposition of α -trimethylsilyl onium salts. In particular, Schmidbauer's study of the reaction of silyl-substituted ylide 5 with methanol left little doubt that nucleophilic desilylation had occurred from phosphonium salt 6 to ylide 7.⁵ Peterson had also



demonstrated an example of mechanistically related sulfonium ylide formation, although the starting sulfonium salt contained an α -stannyl (not silyl) substituent.⁶

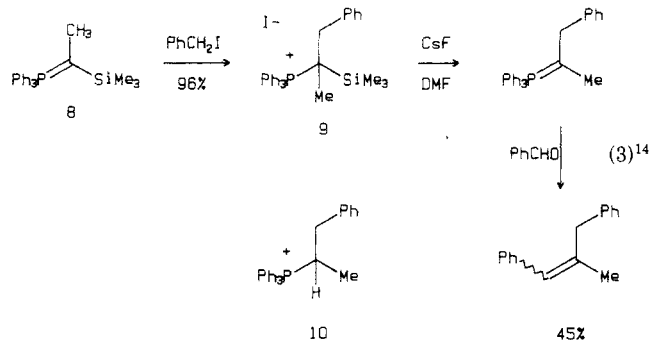
The kinetic reactivity of the C-Si bond in the known α -silyl onium salts was encouraging, but there were also some indications that nucleophilic counterions might induce premature desilylation.⁷ To control this potential problem, we chose to study onium salts having triflate as counterion. Such salts are easily prepared by the alkylation of amines, phosphines, sulfides, imines, etc., with the triflate reagent $Me_3SiCH_2OSO_2CF_3$.^{4,8} In some examples, an alternative procedure using commercially available Me_3SiCH_2Cl (or the corresponding iodide)⁹ is also effective. This works best with anionic nucleophiles such as mercaptides, amide anions, etc., and the onium salt is prepared in a second step by alkylation with alkyl triflate:



Onium salt desilylation has been described using a variety of nucleophiles, including hydroxide, water, chloride, LiAlH_4 , amide anion, and so on.^{7,10,11} However, fluoride ion is the best "silaphile" for ylide generation, and CsF is the reagent of choice. Organic fluoride donors such as " $\text{Bu}_4\text{N}^+\text{F}^-$ " are not satisfactory because they tend to contain water or the bifluoride (F_2H^-) ion, contaminants which can protonate basic ylides.¹² All naked fluoride sources are highly hygroscopic, but CsF has the advantage that it can be vacuum-dried over a small Bunsen flame without significant decomposition. By comparison to KF , CsF is about 10 times more soluble in organic solvents and does not require phase-transfer catalysis to induce desilylation.¹³ Typical reactions are performed by stirring a suspension of CsF in dry acetonitrile or ether solvents with the onium salts at room temperature. The high nucleophilic reactivity of fluoride ion precludes use of halogenated solvents in most cases.

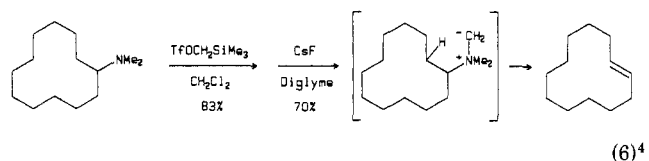
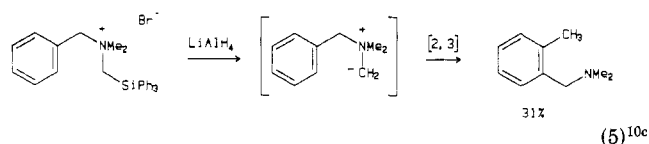
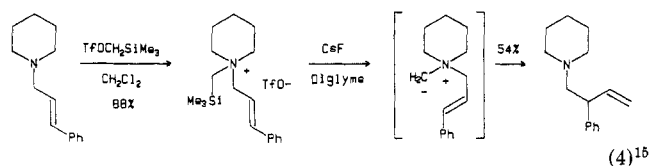
With suitable precautions, anhydrous CsF converts $\text{Ph}_3\text{P}^+\text{CH}_2\text{SiMe}_3 \text{OTf}$ into the yellow ylide $\text{Ph}_3\text{P}=\text{CH}_2$.⁴ When this experiment is performed in the presence of 4-*tert*-butylcyclohexanone, a 70% yield of the Wittig product 4-*tert*-butylmethylenecyclohexane is formed. In contrast, tetrabutylammonium fluoride (presumably contaminated by water and/or F_2H^-) is reported to give 60% of the protodesilylation product $\text{Ph}_3\text{P}^+\text{CH}_3$ and only 18% of the Wittig alkene using benzophenone for in situ ylide trapping.¹¹

There is usually no advantage in the desilylation route vs. the deprotonation route for simple phosphorus ylides if the conventional phosphonium salt is available. However, in cases where direct P-alkylation does not work well, a silicon-mediated approach may be preferred. Branched phosphonium salts such as 10 (eq 3) are difficult to prepare by P-alkylation, but the corresponding α -silyl salt 9 can be made by C-alkylation of silyl-substituted ylide 8.¹⁴ Treatment of 9 with CsF



in dimethylformamide followed by addition of an aldehyde then gives the alkene. Several unbranched ylides have also been prepared in this way and their reactions with aldehydes follow the usual trend for cis olefin selectivity.¹⁴

Access to nonstabilized ammonium ylides via the desilylation method has been demonstrated in several typical examples involving intramolecular ylide reactions (eq 4–6).^{4,15} Amine alkylation with $\text{Me}_3\text{SiCH}_2\text{OTf}$ is especially easy, but the desilylation step can be subtle. Protodesilylation becomes the dominant reaction in acetonitrile, presumably because of the greater basicity of ammonium ylides compared to their phosphorus analogues. This problem can be avoided in diglyme, but reactions are slow due to the limited solubility of the

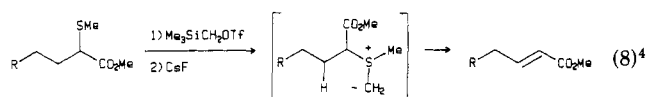
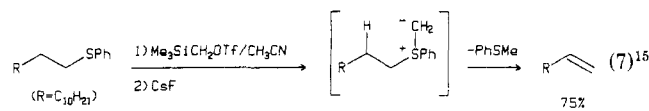


ammonium salt, as well as of CsF , in ether solvents. Nevertheless, reasonable yields of ylide products are observed.

The mild α,β -elimination of eq 6 is especially promising.⁴ Previous examples of ammonium ylide eliminations required phenyllithium or KOT-Bu to achieve the same result. The Sommelet-Hauser rearrangements ([2,3]-sigmatropic shifts) of eq 4 and 5 are also interesting.^{4,15} The example of eq 5 is relatively inefficient, but the unusual conditions (LiAlH_4 cleavage of Ph_3Si) may be responsible for atypical side reactions.^{10c}

Among systems studied so far, the ammonium ylides of eq 4–6 are probably the most demanding test cases for fluoride-induced desilylation. There is also some indication that analogous oxonium ylides can be generated in the same way, but so far the evidence centers on decomposition reactions consistent with transient ylides rather than on characteristic rearrangements.¹⁶

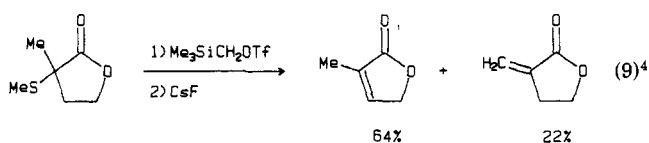
The advantages of ylide generation by desilylation are most readily apparent in the sulfonium series. Protodesilylation is not a severe problem, and the overall sequence from sulfide to ylide can be performed in acetonitrile without isolation of intermediates. Several efficient examples of sulfide conversion into alkene by α,β -elimination are summarized in eq 7–9.^{4,15} All of



$\text{R} = \text{C}_2\text{H}_5$, 81%

$\text{R} = \text{THPO}(\text{CH}_2)_2\text{CH}=\text{CH}_2$, 85%

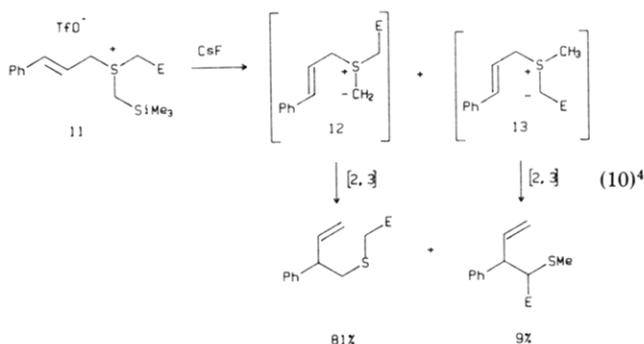
$\text{R} = \text{THPO}(\text{CH}_2)_2\text{CH}=\text{CH}_2$, 63%



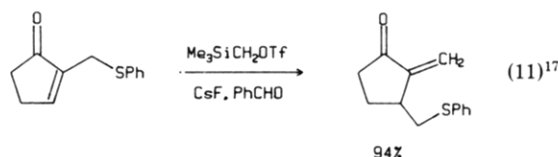
the examples of eq 8 involve elimination by a nonstabilized methylenide even though an ester-stabilized ylide could have been produced by proton transfer. The good yields of alkene products suggest that such equilibration

is not substantial, but the formation of some of the stable ylide cannot be ruled out.

The experiment described in eq 10 gives more quan-



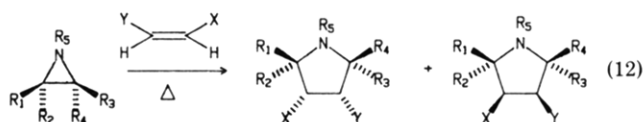
titative information on the possibility of ylide equilibration. Fluoride treatment of 11 affords 81% of the [2,3]-shift product from the kinetic ylide 12 and only 9% of the analogous product from the stabilized ylide 13. Thus, a useful ratio of products can be obtained from the *thermodynamically less stable* ylide.⁴ A similar example of a [2,3]-shift is described in eq 11 where



the product is a sensitive methylenecyclopentanone. The excellent yield reflects a carefully optimized procedure using excess $\text{Me}_3\text{SiCH}_2\text{OTf}$, CsF , and added benzaldehyde to drain off any product-derived methylene species.¹⁷

By far the most extensively studied application of the desilylation method is in the generation of azomethine ylides. In contrast to most of the ylides described so far, nonstabilized 1,3-dipoles could not previously be made in representative systems by any method which allowed intermolecular trapping. The desilylation method has now largely solved this problem, at least for the azomethine methylene species which initiated our study of α -silyl onium salts.^{4,15} Some limitations of the more traditional deprotonation method have already been mentioned in connection with one specific example (eq 2), but a more detailed discussion of this and other known methods is presented below because azomethine ylide generation encounters several additional problems.

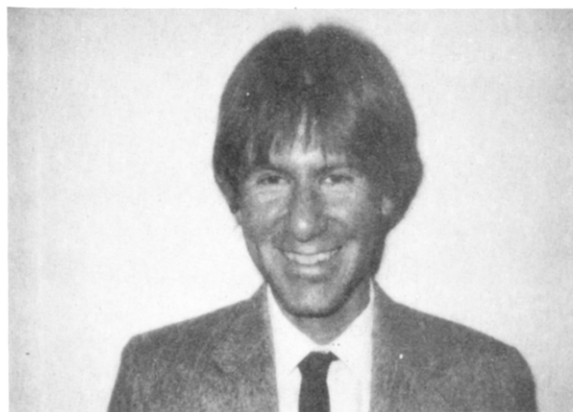
Azomethine ylides have represented attractive synthetic building blocks since the initial observation of reversible thermal conrotatory electrocyclic opening of substituted aziridines and their subsequent trapping.^{18,19} There have been numerous examples of cycloadditions via the aziridine route in the intervening years,²⁰ conforming to the general equation (12); however, it should



be noted that at least one of the substituents R^1 – R^4 must be an effective anion-stabilizing group (electron-withdrawing or conjugating) for the ring-opening step to take place. Thus, although the aziridine approach is conceptually attractive, it is not applicable to targets



Edwin Vedejs was born in Riga, Latvia, on January 31, 1941. His family emigrated to Germany (1944) and then to the U.S. in 1950. Professor Vedejs received his B.S. from the University of Michigan and his Ph.D. from Wisconsin with H. Muxfeldt. After a postdoctoral year with E. J. Corey, he returned to Wisconsin (1967). His research interests include ylides of S, N, and P, unusual rings and functional groups, stereochemistry, and complex total synthesis.

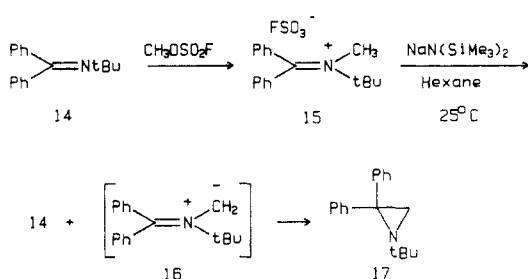
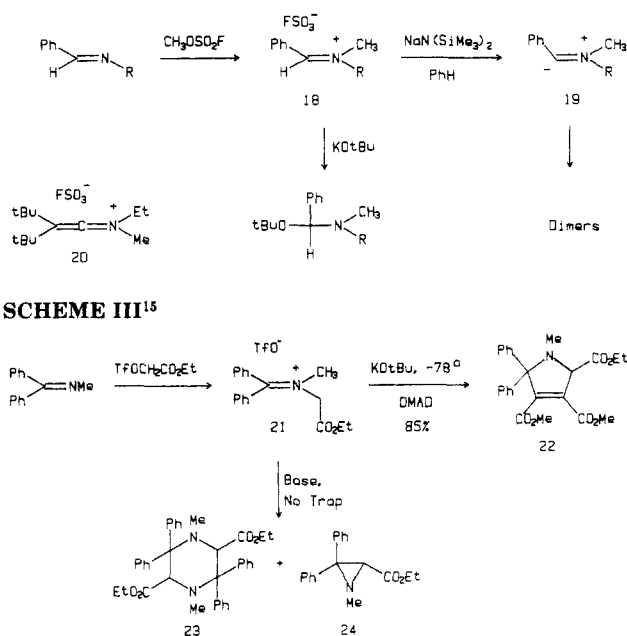
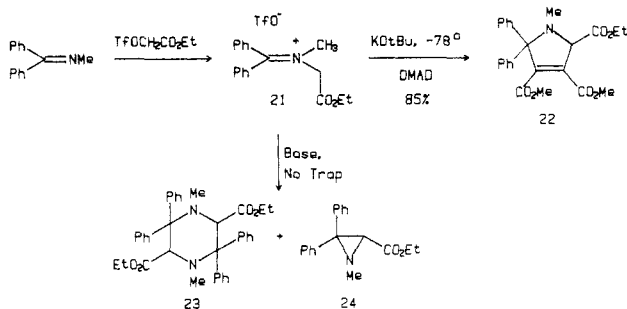


Frederick G. West was born and raised in Safford, AZ, and received his B.S. from the University of Arizona. He received his Ph.D. from the University of Wisconsin (1986) after performing doctoral research in the area of synthetic applications of azomethine ylides. Dr. West is currently a postdoctoral fellow at Columbia University.

containing no stabilizing substituents α to nitrogen.

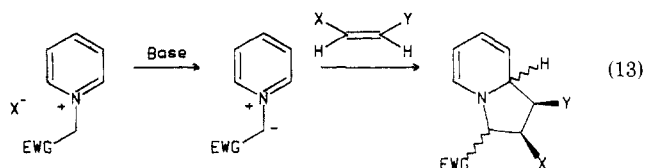
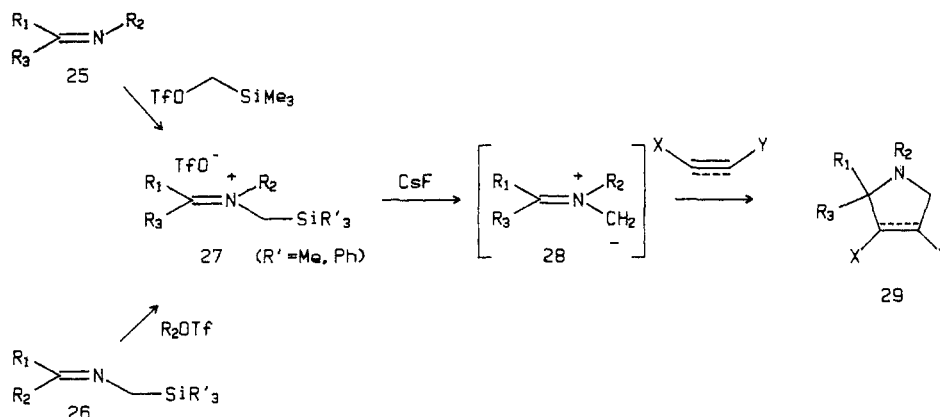
Photochemical electrocyclicization of di-II-amines has been shown to produce transient azomethine ylides.²¹ With a few exceptions,²² however, these ylides have not been trapped with a dipolarophile. The usual reaction pathway involves a suprafacial [1,4] hydrogen shift, often to restore disrupted aromaticity in one of the II components. This method is also restricted to a fairly specialized group of substrates.

The most direct approach to azomethine ylides would seem to be that involving base deprotonation of iminium salts, in analogy to phosphonium, sulfonium, and ammonium ylide procedures. The unsaturation present in iminium salts presents certain inherent difficulties which are not present in the other onium salts. Nucleophilic addition of base at carbon (vide infra) as well as α -deprotonation to give enamine (vide supra) are both possible competing pathways. Since 1,3-dipoles undergo cycloaddition, dimerization is also a legitimate concern,^{18a} as is ylide condensation with the iminium salt precursor. These side-reactions suggest that ideal conditions for base-mediated ylide generation would

SCHEME I^{26A}SCHEME II^{26A,C}SCHEME III¹⁵

include a nonnucleophilic base, an iminium precursor with no "enolizable" α -protons, and the presence of dipolarophile during deprotonation to intercept the 1,3-dipole before alternative cycloadditions can take place.

These requirements are met quite nicely in the case of stabilized heterocyclic aromatic onium ylides. Pyridinium,²³ thiazolium,²⁴ and isoquinolinium²⁵ salts have all been effectively applied to ylide formation, and potassium carbonate or amine bases are usually sufficient for deprotonation (see eq 13). Cycloaddition is facile despite the resultant loss of aromaticity. Azomethine ylides of this sort are useful when the desired adduct contains one or more rings in addition to that

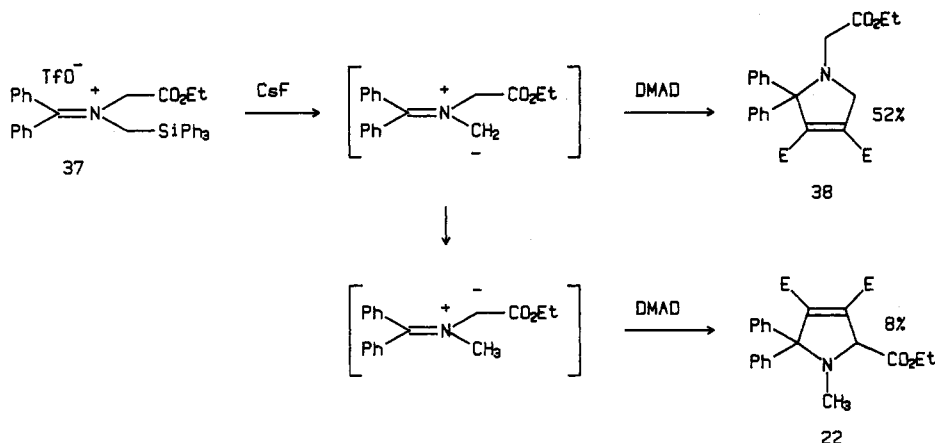
SCHEME IV¹⁵

formed in the cycloaddition and one or more electron-withdrawing groups α to the nitrogen, but simpler products are not readily available.

The versatility of the deprotonation approach would be enhanced if one were able to deprotonate simple acyclic iminium salts containing no anion-stabilizing groups. This technique has been used successfully by Deyrup²⁶ in a small number of examples. Alkylation of benzophenone imine 14 (Scheme I) with methyl fluorosulfonate gave iminium salt 15. (Use of the nonnucleophilic counterion FSO_3^- was necessary to avoid competing N-dealkylation.) Treatment of 15 with a variety of strong bases gave mixtures of dealkylation product 14 and aziridine 17, which results from electrocyclic closure of the intermediate azomethine ylide 16. Unfortunately, under optimum aziridine-forming conditions ($\text{NaN}(\text{TMS})_2/\text{hexane}$) no cycloadducts were seen when the reaction was performed in the presence of norbornene,²⁷ although cycloaddition was observed in the case of a related keteniminium salt 20^{26c} (Scheme II). The less hindered aldiminium salts 18 suffered nucleophilic addition of base or loss of the vinylic proton to give ylide 19.

The analogous ester-substituted iminium salt 21 can be easily prepared by alkylation of the *N*-methylimine with the triflate derived from ethyl glycolate¹⁵ (Scheme III). Deprotonation with either sodium hydride or potassium *tert*-butoxide generates the stabilized ylide, which can be trapped as the dimethyl acetylenedicarboxylate adduct 22 or allowed to form a mixture of dimer 23 and aziridine 24 in the absence of a trap. In the case of $\text{KO}-t\text{-Bu}$ deprotonation the ylide is formed at -78°C , followed after 5 min by addition of the base-sensitive dipolarophile. Although these results suggest the possibility of similarly preforming nonstabilized ylides prior to exposure to trap, their presumed brief lifetime makes nonbasic generation in the presence of dipolarophile a more attractive option. The desilylation method satisfies this as well as other important requirements.

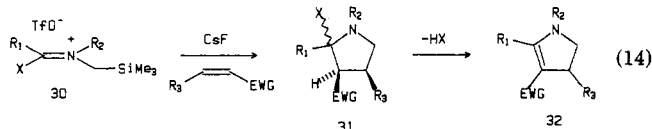
Out of the many possible approaches to the desired α -silyliminium salts, sequential alkylation of imine precursors with the convenient $\text{Me}_3\text{SiCH}_2\text{OTf}$ and ylide

SCHEME V¹⁵

generation with fluoride ion in discrete steps was the first method investigated to generate the transient ylide intermediates, as in **25** \rightarrow **27** \rightarrow **28** (Scheme IV). (See Table I for variations of this approach.) Alternatively, simple alkyl triflates could be used in the case of imines **26** which already contained an α -silyl group and gave the same iminium salts **27**. Fluoride-induced desilylation under a variety of conditions (anhydrous cesium fluoride in acetonitrile or 1,2-dimethoxyethane) afforded the nonstabilized azomethine ylides **28** which were trapped in situ with several dipolarophiles to give cycloadducts **29** in fair to excellent yield.¹⁵

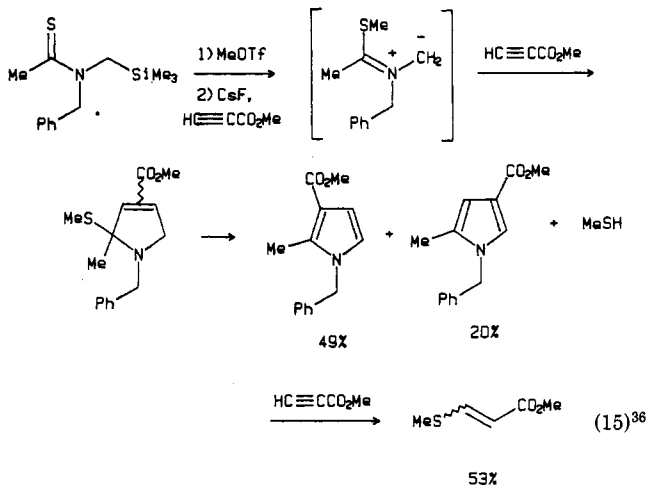
The benzophenone imines used in the early studies work well,¹⁵ but the procedure is not restricted to these substrates. Many types of carbon-nitrogen double bonds are amenable to triflate alkylation/fluoride desilylation, including other simple imines,^{15,28} imidates and thioimidates,^{15,29} amidines,³⁰ vinylogous imidates and thioimidates,²⁹ and several aromatic nitrogen heterocycles. Pyridinium,^{31,32} oxazolium,³³ and thiazolium^{33,34} ylides have been prepared but, with one exception,³⁴ are reported to undergo [3 + 2] cycloaddition only with acetylenic traps. Pyridinium methylides appear to give conjugate addition products with olefinic acceptors.^{31,35} In most cases cesium fluoride is the desilylation reagent of choice. In the case of nonaromatic ylides, typical electron-deficient dipolarophiles, both olefinic and acetylenic, are suitable, but simple olefins are not sufficiently reactive for their cycloaddition to compete effectively with various uncharacterized ylide decomposition pathways.

With a few exceptions, unsymmetrical dipolarophiles give a single regioisomeric cycloadduct. Assuming that cycloaddition regiochemistry is dipole HOMO-controlled, the typical orientation (e.g., eq 14) implies that the largest coefficient of the dipole HOMO lies on the unsubstituted carbon to which the silyl group had been attached.^{19d} The same trend is seen with substrates



(e.g., **30**, eq 14) having heteroatom donor groups directly attached to the 1,3-dipole (i.e., imidates, thioimidates (Table I), amidines, amides, or thioamides (Table II)). All of these dipoles give a nonisolable initial cycloadduct **31** which eliminates the hetero substituent to produce

32, presumably with nitrogen assistance. Conjugation of nitrogen to an electron-withdrawing group, or aromatization to pyrrole in the case of acetylenic adducts, provides the driving force for the elimination. When sulfur is the heteroatom, the eliminated mercaptan is usually scavenged by a 1,4-addition to excess dipolarophile³⁶ (e.g., eq 15), which may explain the consist-



ently higher yields (vide infra) seen with thioimide ylides relative to the imidate analogues, from which an alcohol is eliminated and accumulates in the reaction mixture.

Several examples are worth more careful note. The deprotonation regiochemistry question is addressed in a number of cases, such as iminium salts **33** (eq 16);

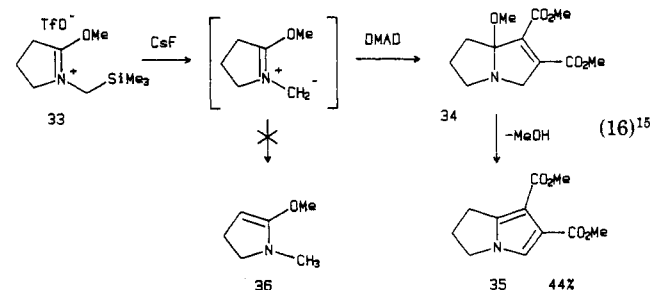


Table I) and **37** (Scheme V; Table I), both of which have other acidic sites in the same molecule. Imidate salt **33** produced cycloadduct **35** via **34** in modest yield (44%), but showed no evidence of proton transfer to give enamine **36** (cf. eq 2). On the other hand, the nonstabilized ylide derived from **37** did produce a small amount (ratio \leq 1:6) of the previously prepared stabi-

TABLE I. N-Alkylation Approaches

A.

entry	R ₁	R ₂	R ₃	sol _{v1}	sol _{v2}	trap	yield, %	ref
1.	Ph	Me	H	CH ₃ CN	CH ₃ CN	DMAD ^d	70	15
2.	Ph(CH ₂) ₂	<i>t</i> -Bu	H	CH ₃ CN	CH ₃ CN	DMAD	45	15
3.	Ph(CH ₂) ₂	<i>t</i> -Bu	H	CH ₃ CN	CH ₃ CN	CH ₂ =CClCN	55 ^a	15
4.	PhCH ₂	Me	PhCH ₂	CH ₂ Cl ₂	DME	DMAD	48	15
5.	Ph(MeS)C=CH	PhCH ₂	H	DME	DME	DMAD	36	29a
6.	-CH ₂ CH ₂ CH ₂ -		H	DME	DME	CH ₂ =CHE	28	28
7.	-CH ₂ CH ₂ CH ₂ -		H	DME	DME	CH ₂ =CHE	30	28
8.	-CH ₂ CH ₂ CH ₂ -		H	DME	DME	DMAD	20	28
9.	-CH ₂ CH ₂ CH ₂ -		H	DME	DME	NMMI	31	28
10.	-CH ₂ CH ₂ CH ₂ CH ₂ -		H	DME	DME	DMAD	20	28
11.	-CH ₂ CH ₂ CH ₂ CH ₂ -		H	DME	DME	NMMI	15	28

B.

entry	Z	sol _{v1}	sol _{v2}	trap	yield, %	ref
1.	MeO	DME	DME	CH ₂ =CHE	85	29a,b
2.	MeO	DME	DME	HC≡CE	70	29b
3.	MeS	DME	DME	HC≡CE	70	29b
4.	MeS	DME	DME	CH ₂ =CHE	68 ^b	29b
5.	MeS	DME	DME	<i>cis</i> -ECH=CHE	75 ^b	29b
6.	MeS	DME	DME	<i>trans</i> -ECH=CHE	87 ^b	29b
7.	MeS	DME	DME	DMAD	80	29b

C.

entry	R ₁	R ₂	R ₃	sol _{v1}	sol _{v2}	F ⁻ source	yield, %	ref
1.	H	H	H	DME	DME	Bu ₄ NF	38	31
2.	H	H	H	CH ₂ Cl ₂	DME ^c	CsF	82	32
3.	Me	H	H	CH ₂ Cl ₂	DME ^c	CsF	47	32
4.	-(CH ₂) ₄ -	H	H	DME	DME	Bu ₄ NF	37	31
5.	H	-(CH ₂) ₄ -	H	DME	DME	Bu ₄ NF	23	31
6.	H	CF ₃	H	CH ₂ Cl ₂	DME ^c	CsF	53 ^b	32
7.	H	H	CN	CH ₂ Cl ₂	DME ^c	CsF	36	32

D.

entry	R ₂	Z	sol _{v1}	sol _{v2}	trap	yield, %	ref
1.	Me	FSO ₃ ⁻	CH ₂ Cl ₂	CH ₃ CN	DMAD	80	15
2.	Me	FSO ₃ ⁻	CH ₂ Cl ₂	CH ₃ CN	CH ₂ =CHE	90	15
3.	Me	FSO ₃ ⁻	CH ₂ Cl ₂	CH ₃ CN	CH ₂ =CClCN	100	15
4.	Me	FSO ₃ ⁻	CH ₂ Cl ₂	CH ₃ CN	<i>cis</i> -ECH=CHE	28	15
5.	Me	FSO ₃ ⁻	CH ₂ Cl ₂	CH ₃ CN	CH ₃ CH=CHE	<5	15
6.	CH ₂ CO ₂ Et	TfO ⁻	CH ₂ Cl ₂	CH ₃ CN	DMAD	52 ^e	15

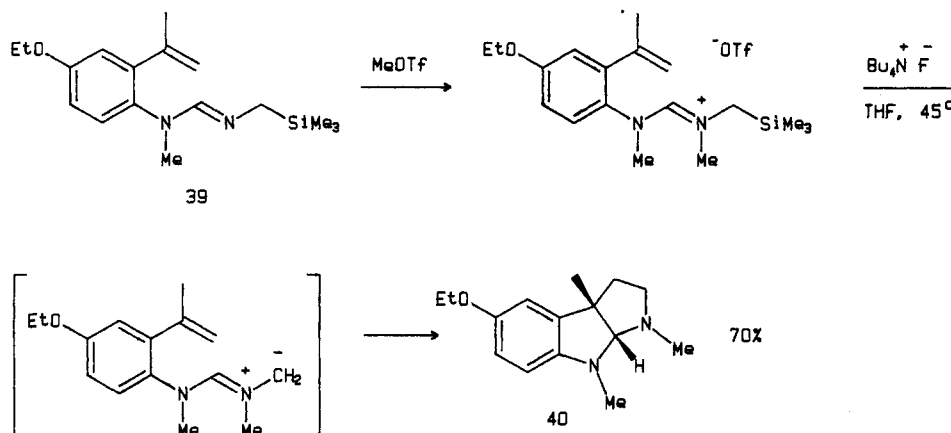
E.

entry	R ₁	R ₂	R ₃ Z	sol _{v1}	sol _{v2}	trap	rxn	yield, %	ref
1.	-CH ₂ CH ₂ CH ₂ -	MeO	MeO	diglyme	diglyme	X = Y = CO ₂ Me	(A)	44	15
2.	-CH ₂ CH ₂ CH ₂ -	MeO	MeO	diglyme	diglyme	X, Y = H, CO ₂ Me	(A)	31	15

TABLE I (Continued)

entry	R ₁	R ₂	R ₃ Z	sol _v 1	sol _v 2	trap	rxn	yield, %	ref
3.	Ph	Me	EtO	DME	DME	X = Y = CO ₂ Me	(A)	45	29a,b
4.	Ph	Me	EtO	DME	DME	X = Y = CO ₂ Me	(B)	48	29a,b
5.	Ph	Me	MeS	DME	DME	X = Y = CO ₂ Me	(B)	74	29a,b
6.	Ph	Me	MeS	DME	DME	X = CO ₂ Me Y = H	(B)	86	29b

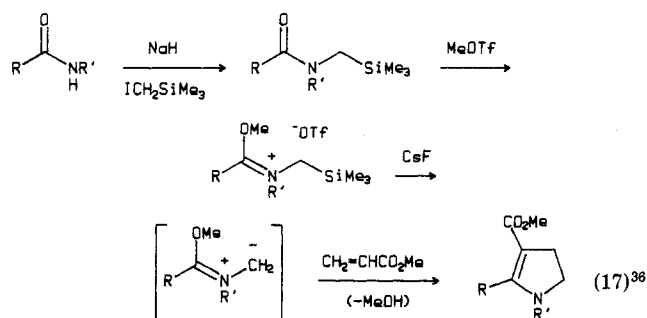
^a Regioisomer mixture. ^b Stereoisomer mixture. ^c Reflux temperature. ^d Abbreviations used: DMAD = EC≡CE, E = CO₂Me, EWG = electron-withdrawing group, OMOM = OCH₂OCH₃, OTBS = OSiMe₂-*t*-Bu, OTf = OSO₂CF₃, Bn = CH₂Ph, NMMI = *N*-Methylmaleimide. ^e 8% of adduct **22** isolated as well.

SCHEME VI³⁰

lized ylide cycloadduct **22** along with the desired adduct **38**.¹⁵ This system resembles the sulfur ylide example of eq 10 and again shows that the thermodynamically less stable ylide can be generated selectively and trapped.

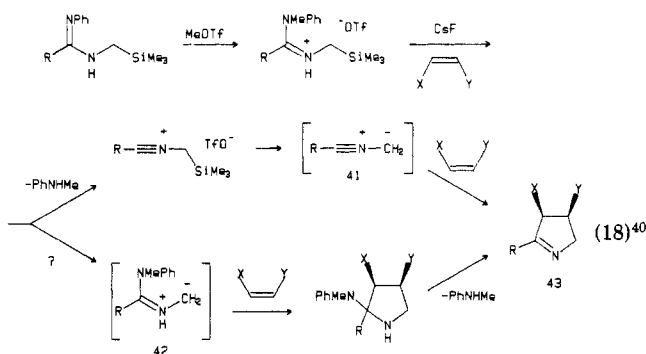
A variant of the *N*-alkylation/desilylation technique has been applied by Smith and Livinghouse to a synthesis of (\pm)-eserethrole **40** (Scheme VI).^{30,37} *N*-Alkylation of [(trimethylsilyl)methyl]amidine **39** gave the amidinium salt which was desilylated under fairly strenuous conditions (Bu₄N⁺F⁻/THF/45 °C) to give azomethine ylide. Intramolecular cycloaddition to the unactivated propenyl side chain resulted in a 70% yield of the natural product. Ortho substitution of dipole and dipolarophile may help ylide trapping efficiency by the styrene. However, other attempts at intramolecular trapping of azomethine ylides made by desilylation have been unsuccessful.^{36,29b,54} It is also surprising that Bu₄N⁺F⁻ is so effective in this example and does not lead to extensive protodesilylation.

The most convenient method for generation of imidate-type ylides is by *O*- or *S*-alkylation of amides or thioamides. This simplified route allows trivial *N*-alkylation of the starting amide with ICH₂SiMe₃, followed by salt formation with methyl triflate and treatment with cesium fluoride^{29b,36,38,39} (eq 17; Table II). The



usual unsaturated ester dipolarophiles give good yields

of pyrroles or pyrrolines with the imidate ylides (Table II). Aromatic aldehydes also serve as effective dipolarophiles in certain cases (Table II), giving either oxazolidines or 2-oxazolines.^{29b,40} Cycloaddition yields can be improved significantly by use of the corresponding thioimidate salts³⁶ in many of the pyrrole or pyrroline examples. This is accomplished by the usually quantitative conversion of amide to thioamide (Lawesson reagent), followed by facile *S*-alkylation. Desilylation of an *N*-protonated amidinium salt has been reported (eq 18; Table II),⁴⁰ and the isolation of pyrroline **43**

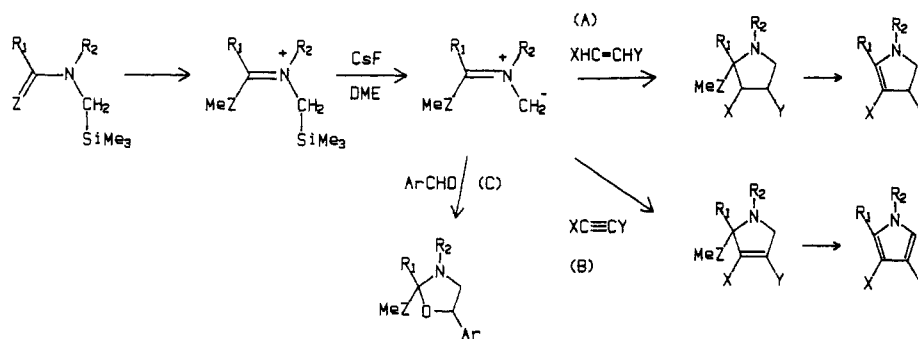


suggests ylide intermediates. This sequence probably involves fluoride-induced elimination of *N*-methyl-aniline followed by formation of nitrile ylide **41** rather than the *N*-protonated azomethine ylide **42** proposed by the authors. However, the timing of amine elimination versus desilylation is not well established. The amide alkylation technology has also been extended to silyl-substituted vinylogous amides to produce adducts analogous to those listed in Table I.⁴¹

The substitution pattern and ring skeleton produced in cycloadducts derived from cyclic azomethine ylides (e.g., eq 16) and acrylate dipolarophiles is well-suited for synthesis of natural product targets among the pyrrolizidine alkaloids. As shown in Scheme VII, the amide *O*-alkylation approach has been successfully applied to the total synthesis of (\pm)-retronecine (**47**)^{38,39}

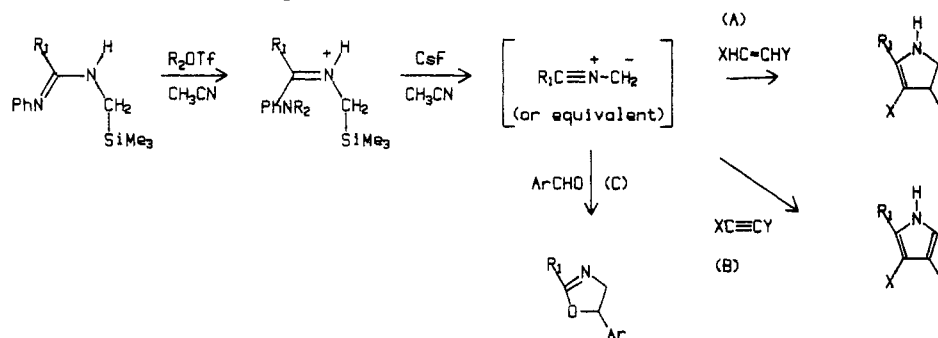
TABLE II. Azomethine Ylides from Amide Derivatives^a

A.



entry	R ₁	R ₂	Z	X	Y	Ar	rxn	yield, %	ref
1.	Me	PhCH ₂	O	CO ₂ CH ₃	H	—	(A)	34	36
2.	Me	PhCH ₂	S	CO ₂ CH ₃	H	—	(A)	53	36
3.	Me	PhCH ₂	S	CO ₂ CH ₃	H	—	(B)	69 ^b	36
4.	CH=CH(CH ₂) ₃	PhCH ₂	O	CO ₂ CH ₃	H	—	(A)	<5	36
5.	CH ₂ =CH(CH ₂) ₃	PhCH ₂	S	CO ₂ CH ₃	H	—	(A)	56	36
6.	—(CH ₂) ₃ —	—	O	CO ₂ CH ₃	H	—	(A)	37	36
7.	—(CH ₂) ₃ —	—	S	CO ₂ CH ₃	H	—	(A)	66	36
8.	—(CH ₂) ₄ —	—	S	CO ₂ CH ₃	H	—	(A)	61	36
9.	—(CH ₂) ₄ —	—	S	CO ₂ CH ₃	H	—	(B)	56 ^b	36
10.	—(CH ₂) ₄ —	—	S	CO ₂ CH ₃	CO ₂ CH ₃	—	(B)	66	36
11.	—CH(OBn)CH ₂ CH ₂ —	—	O	CO ₂ CH ₃	H	—	(A)	51	38
12.	—CH(OMOM)CH ₂ CH ₂ —	—	O	CO ₂ CH ₃	H	—	(A)	41	15
13.	—CH(OTBS)CH ₂ CH ₂ —	—	O	CO ₂ CH ₃	H	—	(A)	31	15
14.	—CH(OBn-NO ₂)CH ₂ CH ₂ —	—	O	CO ₂ CH ₃	H	—	(A)	51	39
15.	Ph	Me	O	CO ₂ CH ₃	CO ₂ CH ₃	—	(B)	58	29b
16.	Ph	PhCH ₂	O	CO ₂ CH ₃	CO ₂ CH ₃	—	(B)	74	29b
17.	Ph	PhCH ₂	O	—	—	—	(C)	64	29b

B.

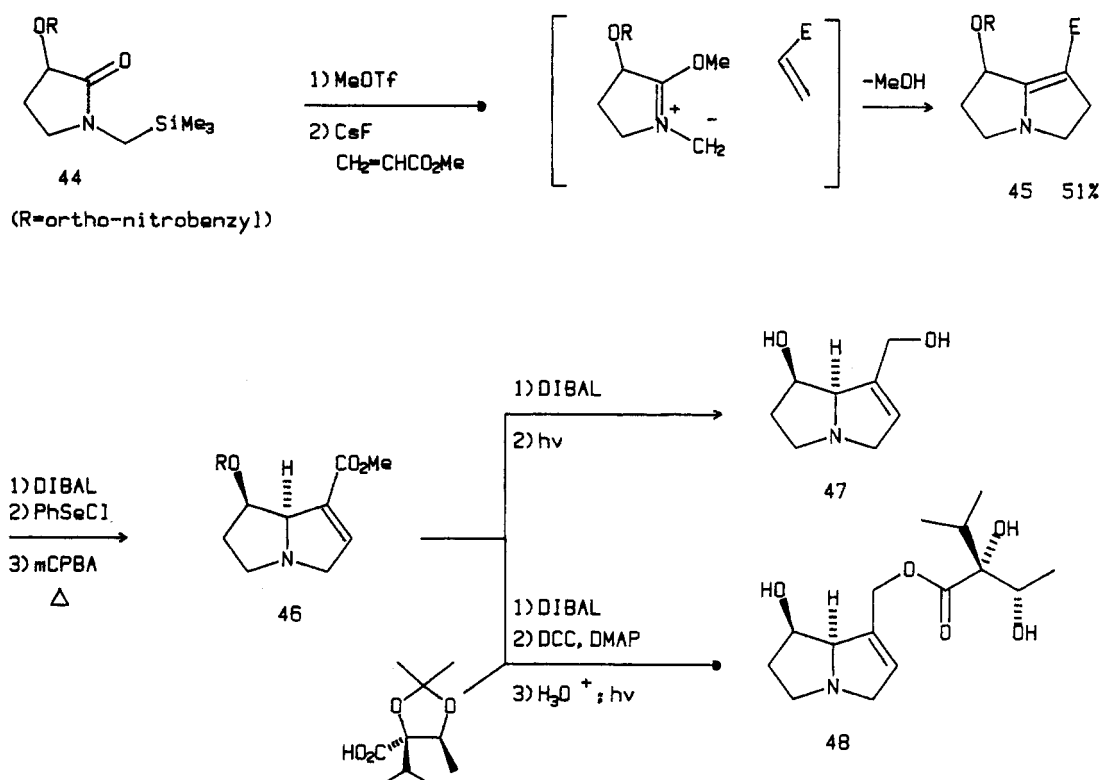


entry	R ₁	R ₂	X	Y	Ar	rxn	yield, %	ref
1.	Me	Me	—CON(Me)CO—	—	—	(A)	82 ^c	40
2.	Me	Me	CO ₂ CH ₃	CO ₂ CH ₃	—	(A)	77	40
3.	Me	Me	CN	CN	—	(A)	51	40
4.	Et	Me	—CON(Me)CO—	—	—	(A)	77 ^c	40
5.	Et	Me	CO ₂ CH ₃	CO ₂ CH ₃	—	(A)	63	40
6.	Et	Me	CN	CN	—	(A)	51	40
7.	nBu	Me	—CON(Me)CO—	—	—	(A)	70 ^c	40
8.	nBu	Me	CO ₂ CH ₃	CO ₂ CH ₃	—	(A)	53	40
9.	nBu	Me	CN	CN	—	(A)	58	40
10.	Ph	Me	—CON(Me)CO—	—	—	(A)	74 ^c	40
11.	Ph	SiMe ₃	CO ₂ CH ₃	CO ₂ CH ₃	—	(A)	67 ^c	40
12.	Ph	SiMe ₃	CN	CN	—	(A)	69	40
13.	Ph	SiMe ₃	CO ₂ CH ₃	CO ₂ CH ₃	—	(B)	64	40
14.	Ph	SiMe ₃	CO ₂ Ph	CO ₂ Ph	—	(B)	44	40
15.	Me	Me	—	—	Ph	(C)	65	40
16.	Me	Me	—	—	2-thienyl	(C)	20	40
17.	Et	Me	—	—	Ph	(C)	50	40
18.	nBu	Me	—	—	Ph	(C)	54	40
19.	nBu	Me	—	—	2-furyl	(C)	46	40
20.	nBu	Me	—	—	2-pyridyl	(C)	64	40
21.	Ph	SiMe ₃	—	—	Ph	(C)	52	40
22.	Ph	SiMe ₃	—	—	2-pyridyl	(C)	62	40

^a See Table I, footnote d for abbreviations. ^b Regioisomer mixture. ^c Product isolated as imine tautomer.

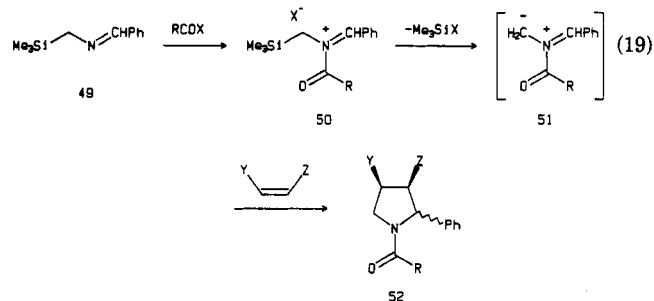
and (±)-indicine (48)³⁹ (Scheme VII). Protected α-hydroxy lactam 44 could be O-methylated in the usual way, followed by treatment with cesium fluoride in the presence of methyl acrylate to give the bicyclic vinylo-

gous carbamate adduct 45 (51% yield). The cycloadduct 45 could be stereospecifically reduced in a 1,4-manner with subsequent selenylation/elimination to unsaturated ester 46 with the correct olefin placement

SCHEME VII^{38,39}

and stereochemistry. Ester reduction to the primary alcohol followed by removal of the secondary hydroxyl protecting group gave retronecine (47), while coupling of the primary hydroxyl with protected trachelanthic acid followed by deprotection gave indicine (48). Substituted analogues of the pyrrolizidine nucleus are also available by this approach.³

An alternative technique for in situ ylide generation involves activation of a [(trimethylsilyl)methyl]imine precursor with acid halides (eq 19; Table III) and

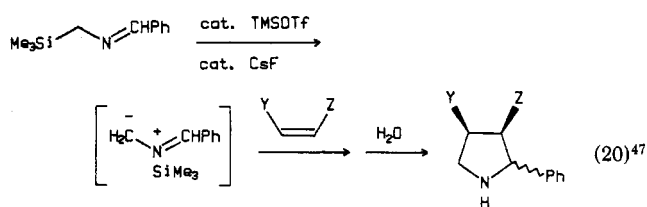


trapping gives *N*-acylpyrrolidines and -pyrrolines. Achiwa and Sekiya⁴²⁻⁴⁴ initially developed this methodology using a variety of acid chlorides. The typical conditions call for slow addition of imine 49 to a mixture of acid chloride plus dipolarophile stirred at a somewhat elevated temperature. The presumed intermediate *N*-acyliminium salt 50 then loses Me_3SiCl to produce the acyl ylide 51. Subsequent [3 + 2] cycloaddition gives the fully saturated *N*-acylpyrrolidine 52, or the *N*-acyl-3-pyrroline in the case of acetylenic dipolarophiles. Livinghouse^{30,37} has successfully applied the corresponding acid fluorides in a similar procedure. As in the case of the previously discussed alkylation methods, the acid halide route requires electron-deficient dipolarophiles (with the exception of one intramolecular case,³⁰ analogous to Scheme VI), and pro-

duces predominantly one regioisomer in the case of unsymmetrical dipolarophiles. It differs from the previously discussed alkylation methods in that desilylation occurs spontaneously and no additional silaphile is necessary.

A further extension has been the use of simple alkyl halides in a comparable reaction, producing *N*-alkylpyrrolidines (Table III).^{45,46} With similar substrates to those applied in the acyl halide case, the imine, alkyl halide, and trap are heated together in hexamethylphosphoramide (HMPA) at 80 °C to produce pyrrolidine directly. At the elevated temperature, halide ion is a sufficiently reactive silaphile to induce ylide formation. In the case of alkyl chlorides, the *N*-unsubstituted product predominates, presumably because Me_3SiCl builds up during initial stages of reaction and competes increasingly well with the relatively unreactive alkyl chloride as an imine activating agent (Scheme VIII).

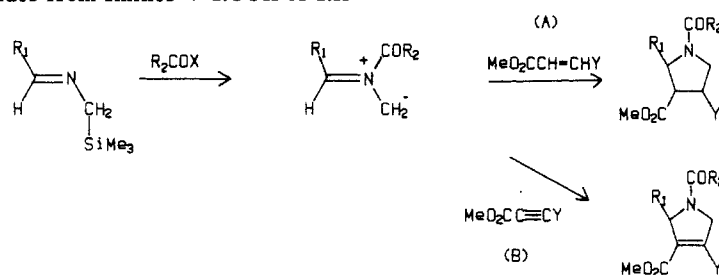
Catalytic imine activation and ylide formation with trimethylsilyl triflate has been demonstrated by the same authors^{47,48} to be a successful azomethine ylide approach in its own right (eq 20; Table IV). As above,



optimum conditions call for mixture of reactants in HMPA at elevated temperature, and it was found that catalytic cesium fluoride accelerated the reaction further. The suggested catalytic sequence involves formation of cesium triflate and trimethylsilyl fluoride,

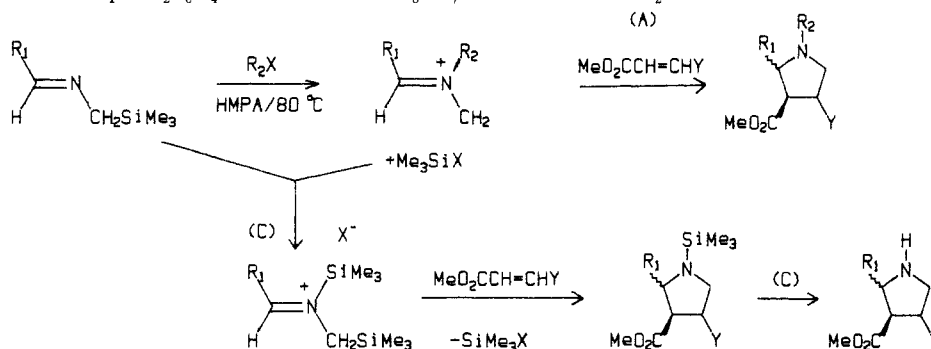
TABLE III. Azomethine Ylides from Iminines + RCOX or RX^a

A.

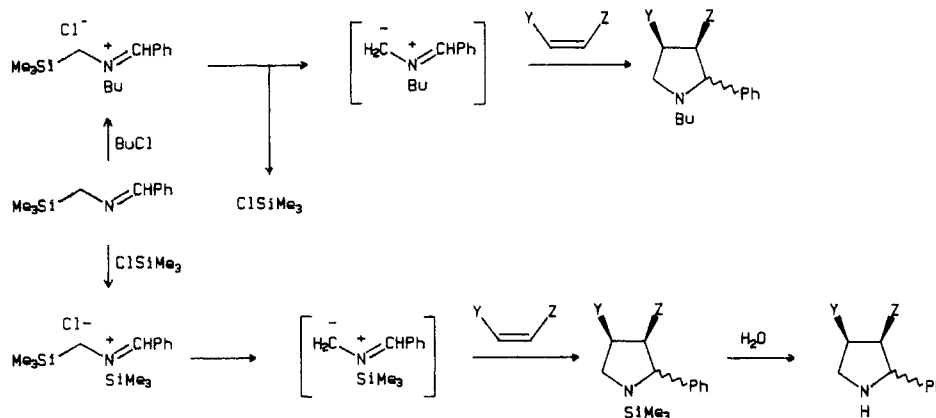


entry	R ₁	R ₂	X	solv/temp, °C	Y	yield, %	rxn	ref
1.	Ph	Ph	Cl	THF/45	CO ₂ Me	85	(B)	42, 43
2.	Ph	PhCH ₂	Cl	THF/45	CO ₂ Me	78	(B)	42, 43
3.	Ph	Me	Cl	THF/45	CO ₂ Me	79	(B)	42, 43
4.	Ph	Ph	Cl	THF/45	H	26	(B)	42, 43
5.	Ph	Ph	Cl	THF/45	CO ₂ Me	81 (1.5:1) ^b	(A)	42, 43
6.	Ph	Ph	Cl	THF/45	H	80 (1.2:1) ^b	(A)	42, 43
7.	Ph	PhCH ₂ O	Cl	THF/45	<i>trans</i> -CO ₂ Me	79 (1.4:1) ^b	(A)	43
8.	Ph	Ph	Cl	THF/45	<i>cis</i> -CO ₂ Me	68 (2:1) ^b	(A)	43
9.	EtS	<i>p</i> -NO ₂ C ₆ H ₄	F	CH ₃ CN/RT	<i>trans</i> -CO ₂ Me	76	(A)	37

B.



entry	R ₁	R ₂	X	Y	yield, %; R ₁ up:down	rxn	ref
1.	Ph	<i>n</i> -Bu	I	<i>trans</i> -CO ₂ Me	82; 3:2	(A)	45
2.	Ph	<i>n</i> -Bu	Cl	<i>trans</i> -CO ₂ Me	76; 1:1.2	(C)	45
3.	Ph	PhCH ₂	Br	<i>trans</i> -CO ₂ Me	79; 1.2:1	(A)	45
4.	Ph	CH ₂ CO ₂ Et	Br	<i>trans</i> -CO ₂ Me	74; 1.1:1	(A)	45
5.	Ph	<i>n</i> -Bu	I	<i>cis</i> -CO ₂ Me	61; 1:2	(A)	45
6.	Ph	<i>n</i> -Bu	Cl	<i>cis</i> -CO ₂ Me	76; 3:7	(C)	45
7.	Ph	<i>n</i> -Bu	I	H	45; 3:2	(A)	45
8.	Ph	<i>n</i> -Bu	Cl	H	65; 1.4:1	(C)	45

^a See Table I, footnote d for abbreviations. ^b *Cis:trans* ratio, R₁ to ester.SCHEME VIII⁴⁵

which disproportionate back to cesium fluoride and trimethylsilyl triflate. The initial cycloadduct is the hydrolytically labile *N*-(trimethylsilyl)pyrrolidine, and the product is isolated as the corresponding *N*-H compound.

N-[(Trimethylsilyl)methyl]imines bearing an anion stabilizing group can be induced to cycloadd in the presence of catalytic trifluoroacetic acid (eq 21; Table

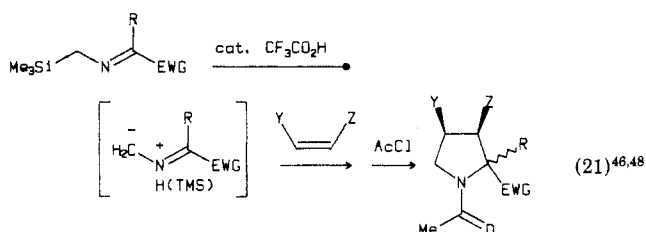
(21)^{46,48}

TABLE IV. Azomethine Ylides via Catalytic Activation of Imines^a

A.

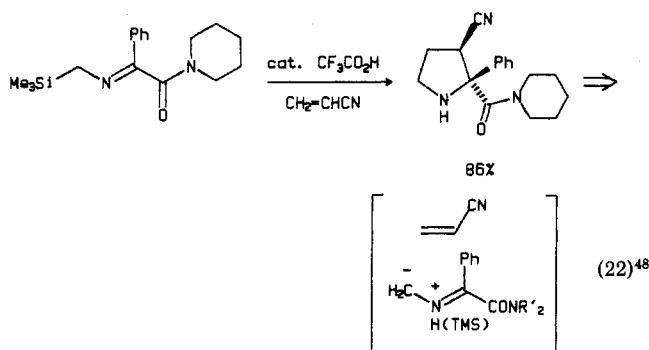
B.

entry	R ₁	R ₂	X	Y	yield, %	ref
1.	Ph	H	CO ₂ Me	<i>trans</i> -CO ₂ Me	91	47
2.	Ph	H	CO ₂ Me	<i>cis</i> -CO ₂ Me	83	47
3.	Ph	H	-CON(Me)CO-		85	47
4.	Ph	H	CO ₂ Me	H	83	47
5.	Ph	(CH ₂) ₅ NC(=O)-	CO ₂ Me	H	94	48
6.	Ph	(CH ₂) ₅ NC(=O)-	CO ₂ Me	<i>trans</i> -CO ₂ Me	94	48
7.	Ph	(CH ₂) ₅ NC(=O)-	CO ₂ Me	<i>cis</i> -CO ₂ Me	69	48

entry	R ₁	R ₂	X	Y	yield, %	ref
1.	Ph	(CH ₂) ₅ NC(=O)-	CO ₂ Me	H	88	48
2.	Ph	(CH ₂) ₅ NC(=O)-	CN	H	86	48
3.	CO ₂ Me	H	CO ₂ Me	CO ₂ Me	49	46
4.	CO ₂ Me	H	CO ₂ Me	<i>cis</i> -CO ₂ Me	27	46
5.	CO ₂ Me	H	CO ₂ Me	<i>trans</i> -Ph	49 ^b	46

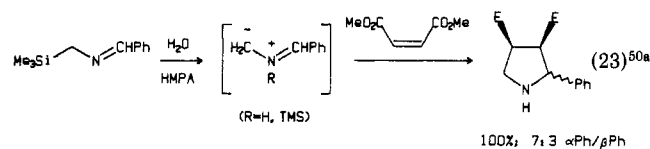
^a See Table I, footnote d for abbreviations. ^b Regioisomer mixture.

IV).^{46,48} The reaction (run in HMPA at ambient temperature) almost certainly produces catalytic trimethylsilyl trifluoroacetate *in situ* but it is not clear whether or not this is the actual activating agent. Interestingly, in the case of monoactivated olefinic dipolarophiles such as acrylonitrile, the regiochemistry of the cycloadduct is similar to that seen with dipoles lacking an electron-withdrawing group (eq 22).⁴⁹ The



cycloadducts are acetylated *in situ* for ease of isolation. Along similar lines, Tsuge⁵⁰ and co-workers have ob-

served apparent azomethine ylide formation induced by water (eq 23). The reaction takes place in HMPA



at room temperature to give cycloadducts in good to excellent yield. In the case of thioimidate substrates, mercaptan elimination probably takes place before cycloaddition (in analogy to eq 18) to give a nitrile ylide cycloadduct.^{50b} These experiments imply significant ylide lifetimes in the presence of at least some water-derived protic species, although mechanistic details are not entirely clear.

A conceptually different route to azomethine ylides involving *in situ* iminium salt formation from aminal derivatives is described in eq 24.⁵¹ Padwa⁵²⁻⁵⁴ has used

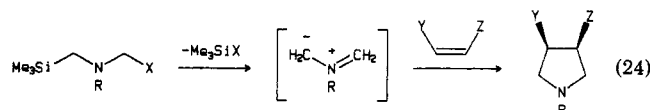
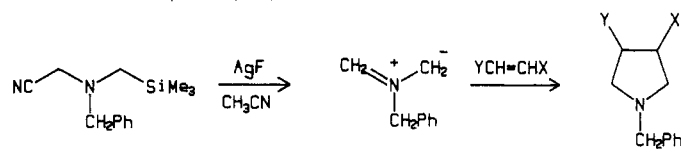


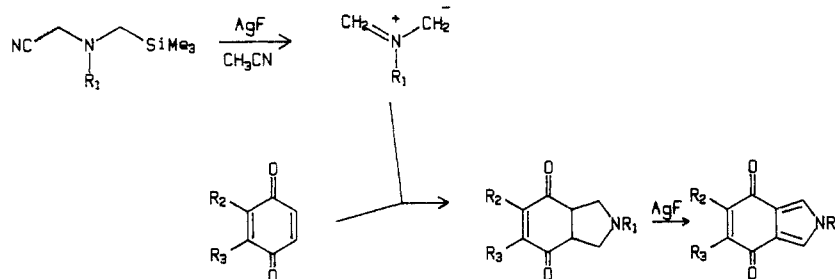
TABLE V. Iminium Salt Generation in Situ (ref 52, 54)^a

A.



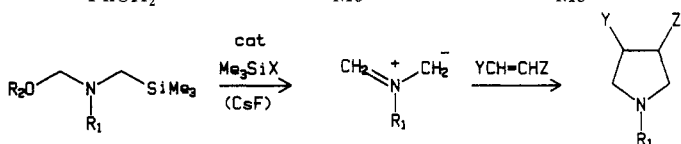
entry	X, Y	yield, %	entry	X, Y	yield, %	entry	X, Y	yield, %
1.	-CON(Ph)CO-	84	4.	CN, CN	69	7.	E-CO ₂ Me, CO ₂ Me	70
2.	Z-CO ₂ Me, CO ₂ Me	23	5.	Ph, CN	33	8.	NO ₂ ,	51
3.	Ph, COMe	42	6.	Ph, CO ₂ Me	45			

B.



entry	R ₁	R ₂	R ₃	yield, %
1.	Me	H	H	64
2.	Me	Me	Me	72
3.	Me	MeO	Me	68
4.	PhCH ₂	H	H	60
5.	PhCH ₂	Me	Me	75

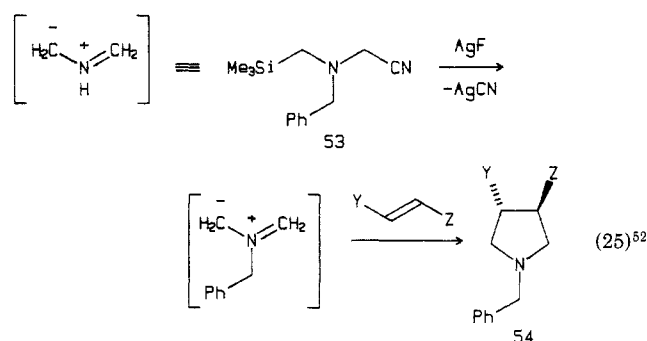
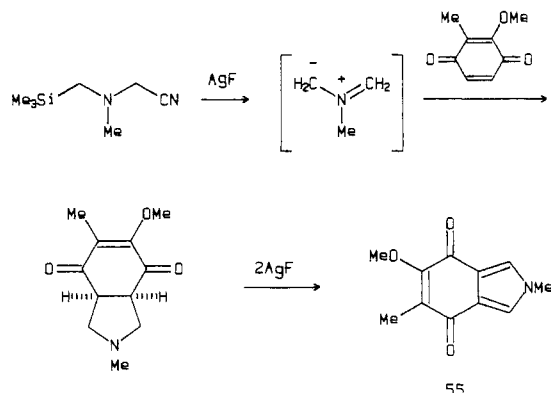
C.



entry	R ₁	R ₂	X	solv	temp, °C	CsF	Y, Z	yield, %
1.	c-C ₆ H ₁₁	Me	OTf	THF	60	no	trans-CO ₂ Me, CO ₂ Me	58
2.	c-C ₆ H ₁₁	Me	OTf	THF	60	yes	trans-CO ₂ Me, CO ₂ Me	90
3.	c-C ₆ H ₁₁	Me	OTf	CH ₃ CN	60	no	trans-CO ₂ Me, CO ₂ Me	57
4.	c-C ₆ H ₁₁	Me	I	THF	25	no	trans-CO ₂ Me, CO ₂ Me	47
5.	c-C ₆ H ₁₁	Me	OTf	HMPA	70	yes	trans-CO ₂ Me, CO ₂ Me	83
6.	c-C ₆ H ₁₁	Me	OTf	THF	60	yes	cis-CO ₂ Me, CO ₂ Me	72
7.	c-C ₆ H ₁₁	Me	OTf	THF	60	yes	H, CO ₂ Me	80
8.	PhCH ₂	Me	OTf	CH ₃ CN	60	no	trans-CO ₂ Me, CO ₂ Me	74
9.	PhCH ₂	Me	OTf	THF	60	yes	trans-CO ₂ Me, CO ₂ Me	83
10.	PhCH ₂	Me	OTf	THF	60	yes	cis-CO ₂ Me, CO ₂ Me	83
11.	PhCH ₂	Me	OTf	THF	60	yes	H, CO ₂ Me	85
12.	PhCH ₂	n-Bu	I	CH ₃ CN	50	yes	trans-CO ₂ Me, CO ₂ Me	75
13.	PhCH ₂	n-Bu	I	CH ₃ CN	60	yes	H, CO ₂ Me	91
14.	PhCH ₂	n-Bu	I	CH ₃ CN	50	yes	trans-Ph, COMe	68
15.	PhCH ₂	n-Bu	I	CH ₃ CN	60	yes	trans-Ph, CO ₂ Me	56

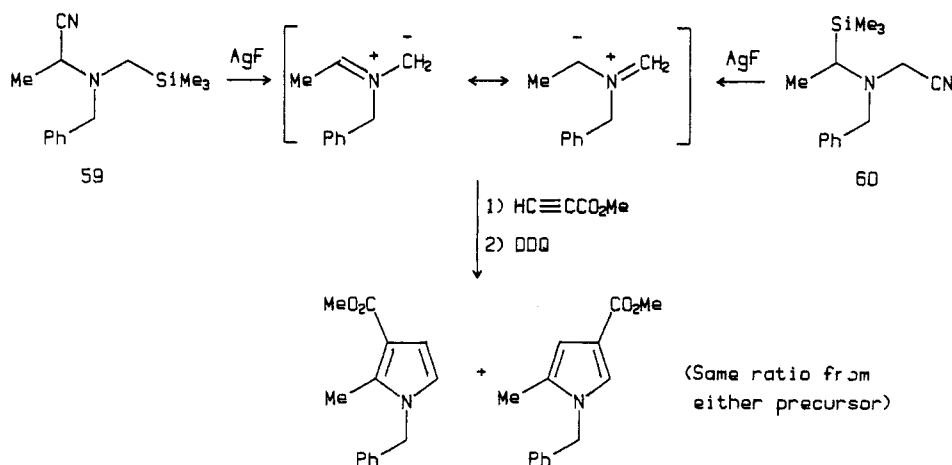
^a See Table I, footnote d for abbreviations.

α -(cyanomethyl)amino silanes (silyl amino nitriles) such as **53** (eq 25; Table V) as convenient azomethine

SCHEME IX⁵³

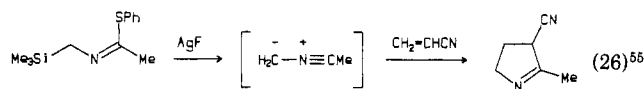
ylide precursors. Exposure to an equivalent of silver fluoride promotes metal-assisted decyanation to an iminium salt and concomitant desilylation by fluoride,

giving the unsubstituted 1,3-dipole. Note that subsequent debenzoylation of the cycloadduct **54** renders **53** the synthetic equivalent of a completely unsubstituted

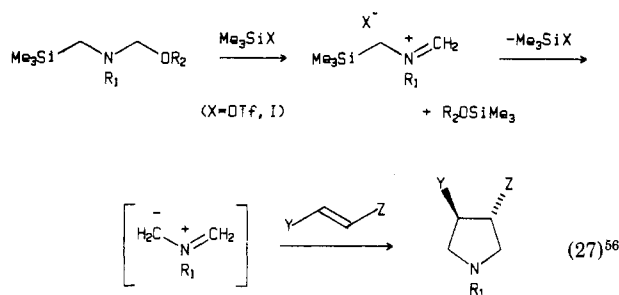
SCHEME X⁵⁴

azomethine ylide. The reaction occurs at room temperature in acetonitrile.

Parker⁵³ and Padwa have applied this method to the synthesis of the *Reniera* isoindole **55** (Scheme IX), as well as other substituted isoindoles (Table VB). Treatment of the *N*-methyl- α -[(cyanomethyl)amino]silane with 5 equiv of AgF in the presence of the appropriately substituted quinone gave the natural product directly in 68% yield. Excess AgF is required to oxidize the intermediate cycloadduct. Turro and Padwa⁵⁵ have used similar conditions to convert *N*-[(trimethylsilyl)methyl] thioimidates into nitrile ylides (eq 26) in experiments that are related to those of Tsuge⁵⁰ et al. (eq 18).

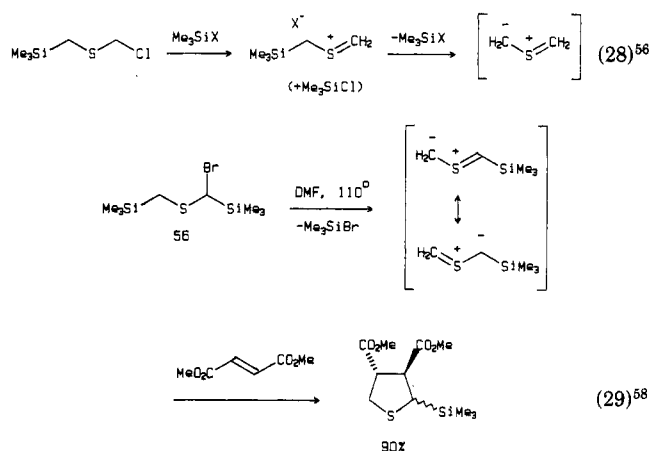


A related procedure is described by Hosomi and Sakurai⁵⁶ who have shown that nonstabilized azomethine ylides can be obtained from *N*-(trimethylsilyl methyl)aminals in the presence of catalytic trimethylsilyl triflate or trimethylsilyl iodide (eq 27; Table V). This

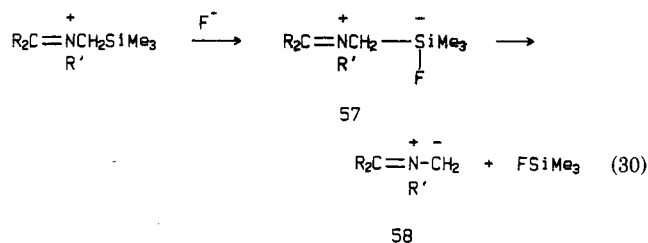


method of activation proceeds in analogy to the first step of the trimethylsilyl triflate mediated substitution reactions of allyl silanes on α -hetero ethers.⁵⁷ The best results are obtained by heating the aminal precursor, dipolarophile, and catalyst in a dipolar aprotic solvent such as tetrahydrofuran (THF) or acetonitrile. The addition of catalytic cesium fluoride usually enhances the yield (see Table V). As in the earlier example, the *N*-benzyl substrate is synthetically equivalent to the parent unsubstituted azomethine ylide. The authors have alluded to formation of thiocarbonyl ylide under analogous conditions (eq 28), and Achiwa et al.⁵⁸ have shown that bis(trimethylsilyl) α -bromo sulfide **56** (eq

29) thermally eliminates trimethylsilyl bromide to give the thiocarbonyl ylide.



Although the starting materials and activation methodology vary, all of the previously discussed nonstabilized ylide reactions involve attack of a nucleophile on a silicon-substituted onium salt intermediate. In any nucleophilic desilylation, the question arises as to whether or not a silicon-free intermediate is responsible for the apparent ylide reactions. A pentavalent silicon species **57** (eq 30) is presumed to pre-



cede ylide **58**, but it is conceivable that electrophiles might react with **57** in a stepwise fashion to give similar products without **58** actually being formed. Contrary evidence is available in the earlier noted observation of characteristic ylide color in the case of (trimethylsilyl)methyl phosphonium salt desilylation and Schmidbauer's ylide isolation experiments. These studies indicate the presence of a silicon-free species for the relatively stable phosphorus ylides. More recently, Padwa et al.^{54a} have shown that the unsymmetrical azomethine ylide precursors **59** and **60** (Scheme X) produce identical ratios of cycloaddition regioisomers with methyl propiolate, providing reasonable evidence

for a common ylide intermediate. Similar conclusions are reached by Achiwa et al. using deuterium-labeled ylide precursors.^{54b} Overall, the evidence is reasonably firm, but not yet conclusive, that silicon-free ylides are indeed generated in the desilylation experiments.

As already mentioned, the extensive study of desilylation in the azomethine ylide area can be attributed to the scarcity of viable methods for generation of the nonstabilized members of this dipole family. Recent work by two groups⁵⁹⁻⁶¹ indicates that treatment of amine *N*-oxides with strong base also produces nonstabilized azomethine intermediates. In contrast to the desilylation route, this method allows 2 + 3 trapping with certain unactivated olefins, apparently because there are no iminium species present to compete in dipole trapping. However, the strongly basic conditions preclude the use of sensitive trapping agents. There are also some reports, describing the generation of nonstabilized azomethines by thermolysis of oxazolidones.⁶²⁻⁶⁶

It is apparent from the many recent contributions in the area that nonstabilized ylides, and particularly the nonstabilized 1,3-dipoles such as azomethine ylides, continue to be of great interest both mechanistically and synthetically. As a means of controllably generating such transient species for either synthetic exploitation or careful study of properties and reactivity, the nucleophilic desilylation of (trimethylsilyl)methyl onium salts offers a powerful tool. Though the field is clearly in its infancy, many useful advances have been made. Systematic examination of such poorly understood factors as onium salt decomposition pathways, desilylation kinetics, and ylide lifetimes, as well as possible alternative fluoride sources, will undoubtedly allow for rational improvements in this group of mostly empirical procedures. Certainly many important applications remain undiscovered. In particular, extension to more highly substituted ylide precursors remains to be studied, as nearly all examples thus far described involve generation of simple methyllide species. Relatively little has been done with the ammonium or sulfonium ylide generation technology. In view of the mild conditions, the desilylation route is most promising for intramolecular ylide trapping and for reactions involving complex substrates. Given the recent explosion of research in this area, one can only assume that the most exciting results in ylide formation by onium salt desilylation are yet to come.

References

- Reviews: Trost, B. M.; Melvin, L. S. *Sulfur Ylides: Emerging Synthetic Intermediates*; Academic: New York, 1975.
- Lepley, A. R.; Giumanini, A. G. *Mech. of Mol. Mig.* **1970**, *3*, 297.
- Vedejs, E.; West, F. G., unpublished results.
- Vedejs, E.; Martinez, G. R. *J. Am. Chem. Soc.* **1979**, *101*, 6452.
- Schmidbaur, H. *Acc. Chem. Res.* **1975**, *8*, 62, and references therein.
- Peterson, D. J. *J. Organomet. Chem.* **1971**, *26*, 215.
- (a) Cooper, G. D. *J. Am. Chem. Soc.* **1954**, *76*, 3713. (b) Miller, N. E. *Inorg. Chem.* **1965**, *4*, 1458. (c) Seyferth, D.; Singh, G. *J. Am. Chem. Soc.* **1965**, *87*, 4156. (d) Musker, W. K.; Stevens, R. R. *Inorg. Chem.* **1969**, *8*, 255. (e) Sato, Y.; Aoyama, Y.; Shirai, H. *J. Organomet. Chem.* **1974**, *82*, 21. (f) Cunico, R. F.; Gill, H. S. *Organometallics* **1982**, *1*, 1.
- Baum, K.; Lerdel, D. A.; Horn, J. C. *J. Org. Chem.* **1978**, *43*, 203.
- Ambesht, S.; Chiu, S. K.; Peterson, P.; Queen, J. *Synthesis* **1980**, 318.
- (a) Sato, Y.; Ban, Y.; Aoyama, T.; Shirai, H. *J. Org. Chem.* **1976**, *41*, 1962. (b) Sato, Y.; Toyooka, T.; Aoyama, T.; Shirai, H. *J. Org. Chem.* **1976**, *41*, 3559. (c) Sato, Y.; Sakakibara, H. *J. Organomet. Chem.* **1979**, *166*, 303.
- Sekiguchi, A.; Ando, W. *J. Org. Chem.* **1979**, *44*, 413.
- (a) Yakobson, G. G.; Akhmetova, N. E. *Synthesis* **1983**, 169. (b) Cox, D. P.; Terpinski, J.; Lawrynowicz, W. *J. Org. Chem.* **1984**, *49*, 3216. (c) Vorbruggen, H.; Krolkiewicz, K. *Tetrahedron Lett.* **1984**, *25*, 1259. (d) Sharma, R. K.; Fry, J. L. *J. Org. Chem.* **1983**, *48*, 2112.
- Wyman, D. A.; Roth, M. M.; Pollard, B. D. *Talanta* **1984**, *31*, 1036.
- (a) Bestmann, H. J.; Dötzer, R.; Manero-Alvarez, J. *Tetrahedron Lett.* **1985**, *26*, 2769; (b) Bestmann, H. J.; Bomhard, A. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 545.
- Martinez, G. R., Ph.D. Dissertation, University of Wisconsin, 1980.
- (a) Olah, G. A.; Doggweiler, H.; Felberg, J. D. *J. Org. Chem.* **1984**, *49*, 2112. (b) Olah, G. A.; Doggweiler, H.; Felberg, J. D. *J. Org. Chem.* **1984**, *49*, 2116. (c) Olah, G. A.; Doggweiler, H.; Felberg, J. D.; Frohlich, S. *J. Org. Chem.* **1985**, *50*, 4847.
- Cohen, T.; Kosarych, Z.; Suzuki, K.; Yu, L.-C. *J. Org. Chem.* **1985**, *50*, 2965.
- (a) Heine, H. W.; Peavy, R. *Tetrahedron Lett.* **1965**, *6*, 3123. (b) Huisgen, R.; Scheer, W.; Szeimies, G.; Huber, H. *Tetrahedron Lett.* **1966**, 397; (c) Huisgen, R.; Scheer, W.; Huber, H. *J. Am. Chem. Soc.* **1967**, *89*, 1753.
- Reviews: (a) Lown, J. W. *Rec. Chem. Prog.* **1971**, *32*, 51. (b) Stukwisch, C. G. *Synthesis* **1973**, 469. (c) Kellogg, R. M. *Tetrahedron* **1976**, *32*, 2165. (d) Lown, J. W. *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1, p 653.
- See reference 19 for many early examples. More recent examples include: (a) Wenkert, D.; Ferguson, S. B.; Porter, B.; Qvarnstrom, A.; McPahil, A. T. *J. Org. Chem.* **1985**, *50*, 4114, and references therein. (b) DeShong, P.; Kell, D. A.; Sidler, D. R. *J. Org. Chem.* **1985**, *50*, 2309, and references therein. (c) DeKimpe, N.; Sulmon, P.; DeBuyck, L.; Verhe, R.; Schamp, N.; Declercq, J.-P.; van Meerseche, M. *J. Chem. Res.* **1984**, 82.
- Reviews: (a) Leone, A. A.; Mariano, P. S. *Rev. Chem. Intermed.* **1981**, *4*, 81. (b) Schultz, A. G. *Acc. Chem. Res.* **1983**, *16*, 210, and references therein.
- Zaima, T.; Matsuno, C.; Matsunaga, Y.; Mitsunashi, K. *J. Heterocycl. Chem.* **1984**, *21*, 445. Zaima, T.; Matsunaga, Y.; Mitsunashi, K. *Ibid.* **1983**, *20*, 1.
- (a) Kakehi, A.; Ito, S. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 938. (b) Ikemi, Y.; Matsumoto, K.; Uchida, T. *Heterocycles* **1983**, *20*, 1009. (c) Tsuge, O.; Kanemasa, S.; Takenaka, S.; Kuroaka, S. *Chemistry Lett.* **1984**, 465.
- (a) Potts, K. T.; Choudhury, D. R.; Westby, T. R. *J. Org. Chem.* **1976**, *41*, 187. (b) Kraus, G. A.; Nagy, J. O. *Tetrahedron Lett.* **1981**, *22*, 2727. (c) Kraus, G. A.; Nagy, J. O. *Ibid.* **1983**, *24*, 3427.
- (a) Toth, G.; Frank, J.; Bende, Z.; Weber, L.; Simon, K. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1961; (b) Tsuge, O.; Kanemasa, S.; Takenaka, S. *Chem. Lett.* **1985**, 355.
- (a) Deyrup, J. A.; Szabo, W. A. *J. Org. Chem.* **1975**, *40*, 2048. (b) Deyrup, C. L.; Deyrup, J. A.; Hamilton, M. *Tetrahedron Lett.* **1977**, *39*, 3437; (c) Deyrup, J. A.; Kuta, G. S. *J. Org. Chem.* **1978**, *43*, 501.
- Typical electron-deficient dipolarophiles were found to be incompatible with the strongly basic reaction medium.
- Terao, Y.; Imai, N.; Achiwa, K.; Sekiya, M. *Chem. Pharm. Bull.* **1982**, *30*, 3167.
- (a) Padwa, A.; Haffmanns, G.; Tomas, M. *Tetrahedron Lett.* **1983**, *24*, 4303. (b) *J. Org. Chem.* **1984**, *49*, 3314.
- Smith, R.; Livinghouse, T. *J. Org. Chem.* **1983**, *48*, 1554.
- Miki, Y.; Hachiken, H.; Takemura, S.; Ikeda, M. *Heterocycles* **1984**, *22*, 701.
- Tsuge, O.; Kanemasa, S.; Kuraoka, S.; Takenaka, S. *Chem. Lett.* **1984**, 279.
- Padwa, A.; Chiacchio, U.; Venkatramanan, M. K. *J. Chem. Soc., Chem. Commun.* **1985**, 1108.
- Tsuge, O.; Kanemasa, S.; Kuraoka, S. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1570.
- Tsuge, O.; Kanemasa, S.; Kuraoka, S.; Takenaka, S. *Chem. Lett.* **1984**, 281.
- Vedejs, E.; West, F. G. *J. Org. Chem.* **1983**, *48*, 4773.
- Livinghouse, T.; Smith, R. *J. Chem. Soc., Chem. Commun.* **1983**, 2, 210. Smith, R.; Livinghouse, T. *Tetrahedron* **1985**, *41*, 3559. For a related approach to carbonyl-stabilized ylides by desilylation, see: Westling, M.; Smith, R.; Livinghouse, T. *J. Org. Chem.* **1986**, *51*, 1159.
- Vedejs, E.; Martinez, G. R. *J. Am. Chem. Soc.* **1980**, *102*, 7993.
- Vedejs, E.; Larsen, S.; West, F. G. *J. Org. Chem.* **1985**, *50*, 2170.
- Tsuge, O.; Kanemasa, S.; Matsuda, K. *Chem. Lett.* **1985**, 1411.
- Chen, S.-F.; Ullrich, J. W.; Mariano, P. S. *J. Am. Chem. Soc.* **1983**, *105*, 6160.
- Achiwa, K.; Sekiya, M. *Chem. Lett.* **1981**, 1213.
- Achiwa, K.; Motoyama, T.; Sekiya, M. *Chem. Pharm. Bull.* **1983**, *31*, 3939.
- Achiwa, K.; Sekiya, M. *Heterocycles* **1983**, *20*, 167.

- (45) Achiwa, K.; Imai, N.; Inaoka, T.; Sekiya, M. *Chem. Pharm. Bull.* **1984**, *32*, 2878.
- (46) Imai, N.; Terao, Y.; Achiwa, K. *Heterocycles* **1985**, *23*, 1107.
- (47) Achiwa, K.; Sekiya, M. *Tetrahedron Lett.* **1982**, *23*, 2589.
- (48) Achiwa, K.; Imai, N.; Motoyama, T.; Sekiya, M. *Chem. Lett.* **1984**, 2041. Achiwa, K.; Sugiyama, K.; Sekiya, M. *Chem. Pharm. Bull.* **1985**, *33*, 1975.
- (49) The opposite regioselectivity was obtained under $\text{Bu}_4\text{N}^+\text{F}^-$ mediated anionic cycloaddition.⁴⁸
- (50) (a) Tsuge, O.; Kanemasa, S.; Hatada, A.; Matsuda, K. *Chem. Lett.* **1984**, 801. (b) Tsuge, O.; Kanemasa, S.; Yamada, T.; Matsuda, K. *Heterocycles* **1985**, *23*, 2489.
- (51) For an example of stabilized azomethine ylides from aminal derivatives, see: Imai, N.; Terao, Y.; Achiwa, K.; Sekiya, M. *Tetrahedron Lett.* **1984**, *25*, 1579.
- (52) Padwa, A.; Chen, Y.-Y. *Tetrahedron Lett.* **1983**, *24*, 3447.
- (53) Parker, K. A.; Cohen, I. S.; Padwa, A.; Dent, W. *Tetrahedron Lett.* **1984**, *25*, 4917.
- (54) (a) Padwa, A.; Chen, Y.-Y.; Dent, W.; Nimmessgern, H. *J. Org. Chem.* **1985**, *50*, 4006. Padwa, A.; Chen, Y.-Y.; Chiacchio, V.; Dent, W. *Tetrahedron* **1985**, *41*, 3529. (b) Terao, Y.; Kotaki, H.; Imai, N.; Achiwa, K. *Chem. Pharm. Bull.* **1985**, *33*, 896.
- (55) Turro, N. J.; Cha, Y.; Gould, I. R.; Padwa, A.; Grasdaska, J. R.; Tomas, M. *J. Org. Chem.* **1985**, *50*, 4417.
- (56) Hosomi, A.; Sakata, Y.; Sakurai, H. *Chem. Lett.* **1984**, 1117.
- (57) Sakurai, H.; Sakata, Y.; Hosomi, A. *Chem. Lett.* **1983**, 409.
- (58) Terao, Y.; Tanaka, M.; Imai, N.; Achiwa, K. *Tetrahedron Lett.* **1985**, *26*, 3011. Aono, M.; Hyodo, C.; Terao, Y.; Achiwa, K. *Ibid.* **1986**, *27*, 4039.
- (59) Beugelmans, R.; Negron, G.; Roussi, G. *J. Chem. Soc., Chem. Commun.* **1983**, 31.
- (60) (a) Beugelmans, R.; Benadjijila-Iguertsira, L.; Chastanet, J.; Negron, G.; Roussi, G. *Can. J. Chem.* **1985**, *63*, 725. (b) Chastanet, J.; Roussi, G. *Heterocycles* **1985**, *23*, 653. (c) Chastanet, J.; Roussi, G. *J. Org. Chem.* **1985**, *50*, 2910.
- (61) Takayama, H.; Nomoto, T. *J. Chem. Soc., Chem. Commun.* **1982**, 408.
- (62) For early evidence of this pathway, see: (a) Rizzi, G. P. *J. Org. Chem.* **1970**, *35*, 2069. (b) Ratts, K. W.; Howe, R. K.; Phillips, W. G. *J. Am. Chem. Soc.* **1969**, *91*, 6115. (c) Quast, H.; Gelléri, A. *Liebigs Ann. Chem.* **1975**, 939.
- (63) Eschenmoser, A. *Chem. Soc. Rev.* **1976**, *5*, 377.
- (64) Burger, K.; Meffert, A.; Bauer, S. *J. Fluorine Chem.* **1977**, *10*, 57.
- (65) (a) Confalone, P. N.; Huie, E. M. *J. Am. Chem. Soc.* **1984**, *106*, 7175. (b) Wang, C.-L.; Ripka, W. C.; Confalone, P. N. *Tetrahedron Lett.* **1984**, *25*, 4613.
- (66) (a) Grigg, R.; Thianpatanagul, S. *J. Chem. Soc., Chem. Commun.* **1984**, 180. (b) Grigg, R.; Aly, M. F.; Sridharan, V.; Thianpatanagul, S. *Ibid.* **1984**, 182.