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Kanemasa, Shuji
Institute of Advanced Material Study Kyushu University

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The Chemistry of Azomethine Ylides Developed in the Institute

Shuji KANEMASA

Dedicated to Professor Otohiko Tsuge on the occasion of his retirement

The research on azomethine ylide 1,3-dipoles, developed in the last five years in the Institute of Advanced Material Study, Kyushu University, is briefly reviewed. New generation methods of unprecedented azomethine ylides, reactivities in their cycloadditions with olefinic dipolarophiles, and stereochemical as well as regiochemical selectivities in the cycloadditions are described.

Azomethine ylides are the 1,3-dipoles with an atomic sequence of carbon-nitrogen-carbon, which undergo cycloadditions with unsaturated carbon-carbon bonds leading to five-membered heterocycles such as pyrrolidines, pyrrolines, and pyrroles. In 1983 when we started our present project, there were quite limited numbers of reports known for generation methods of azomethine ylides. It was about the same time that a wave of new findings merged into the chemistry of azomethine ylides. Conceptually new generations of azomethine ylides such as the desilylation route [1] and the tautomerization route [2] were reported one after another and these works attracted much attention of organic chemists to the chemistry of azomethine ylides.

The present article reviews on the chemistry of azomethine ylide 1,3-dipoles developed in our laboratory, especially on new generation methods of unprecedented azomethine ylides and on reactivities and selectivities in their cycloadditions with olefins.

1. Ylide Generation by Desilylation Method

(Trimethylsilyl)methyl azide (**1**), as a nonexplosive equivalent of methyl azide, was readily accessible from the reaction of commercially available (trimethylsilyl)methyl chloride with sodium azide in HMPA and subsequent distillation. [3] This azide **1** reacts with triphenylphosphine or trialkyl phosphites to produce the corresponding phosphoranes **2**; they undergo condensations with a variety of electrophiles of the carbonyl-related types such as aldehydes, ketones, carbon dioxide, carbon disulfide, isocyanates, isothiocyanates, or ketenes to give *N*-silylmethyl imines **3**, isocyanate **4**, isothiocyanate **5**, carbodiimides **6**, and ketenimines **7** (Scheme 1). [4] As a

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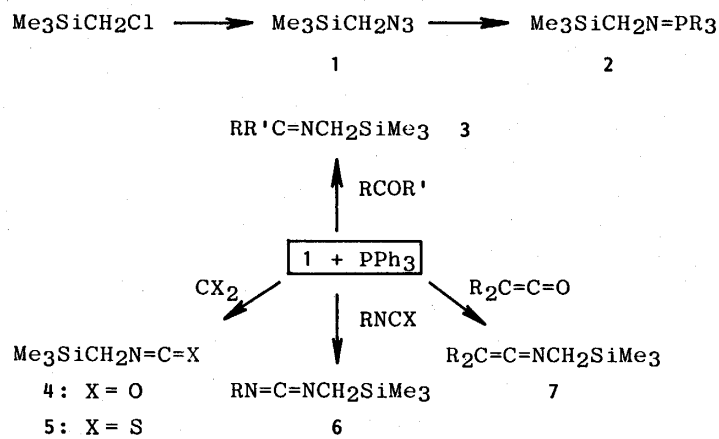
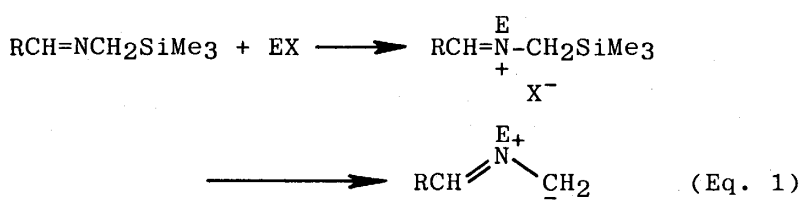
oneflask procedure, azide **1** and carbonyl compounds are simply heated in the presence of an equimolar amount of triphenylphosphine leading to desired *N*-silylmethylated imines **3** and related compounds.



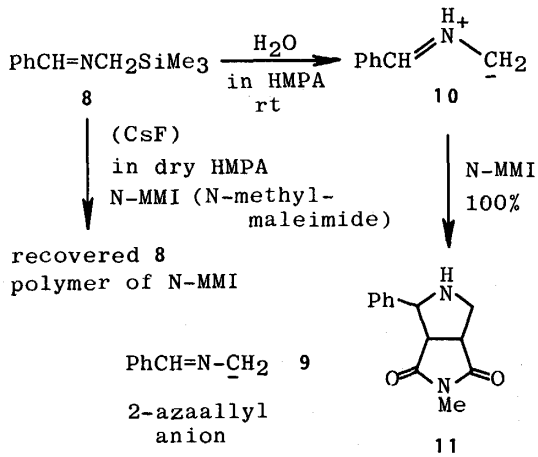
Scheme 1

N-Acylation,[5] *N*-alkylation,[6] *N*-silylation,[7] or *N*-protonation [8] activates *N*-silylmethyl imines so that they can be easily desilylated to generate the corresponding azomethine ylides under mild conditions. This sequence of *N*-quaterization and desilylation consists of the major part of a new generation method of azomethine ylides called the desilylation route (Equation 1).[9] On the other hand, direct desilylation of *N*-benzylidene(trimethylsilyl)methylamine (**8**) with flouoride ion without prior quaterization was expected to be a new entry to 2-azaallyl anion **9** (Scheme 2). However, all attempts to capture the resulting anionic species with *N*-methylmaleimide as an electron-deficient activated olefin were unsuccessful. No cycloadduct was obtained, but instead the maleimide underwent ready polymerization.[10]



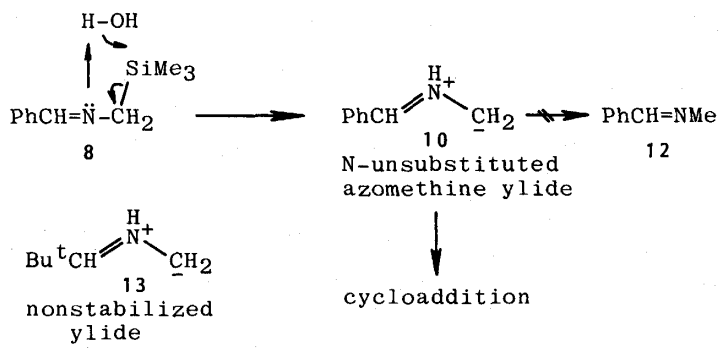
(Eq. 1)

Water was used to suppress polymerization of the maleimide. It was found that *N*-silylmethyl imine **8** could be desilylated by action of water even in the absence of fluoride ion. The anionic species generated was not the 2-azaallyl anion **9** but an azomethine ylide **10** (Scheme 2).[10] This ylide **10** belongs to an unusual azomethine ylide of the *N*-unsubstituted (or *N*-protonated) type and also of the nonstabilized type. Trapping **10** with *N*-methylmaleimide gave the cycloadduct **11** in a quantitative yield.



Scheme 2

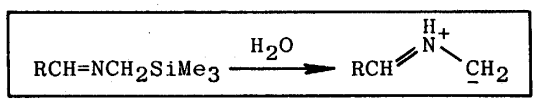
Excess of water, if less than five equivalents, could still serve as an effective desilylating agent and addition of a catalytic amount of acetic acid accelerated the ylide generation. No protodesilylation product, *N*-benzylidenemethylamine (**12**), was even detected when a highly reactive dipolarophile is present under these aqueous generation conditions (Scheme 3).

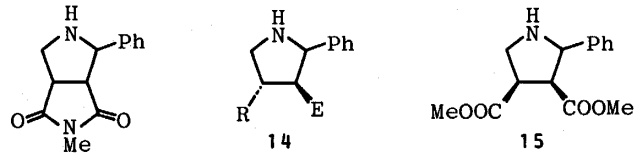


Scheme 3

Some other related ylides including alkyl-substituted derivative **13** can be similarly generated; they undergo clean cycloadditions to a variety of activated oleins to produce *N*-unsubstituted pyrrolidines **11** and **14–17** (Scheme 4).[11]

Thermal or photochemical ring opening of aziridines has been one of the most convenient accesses to azomethine ylides, while at least one electron-withdrawing substituent (EWG) on the ring carbon is requisite for smooth ring opening (Equation 2).[12] The thermal imine-azomethine ylide tautomerism takes place only when α-hydrogen of imines is highly acidic as exemplified by imine esters (Equation 3).[13] The desilylation route[5-9] as well as its variation[14] methods (Equations 1 and 4) can generate nonstabilized azomethine ylides, but the nitrogen is always substituted. Our water-induced desilylation route has an advantage that the *N*-unsubstituted azomethine ylides with no ylide-stabilizing substituent are accessible.



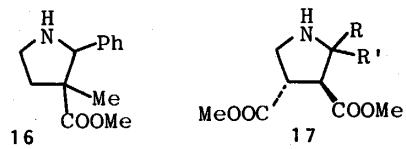


11

14

R = E = COOMe
R = E = CN
R = Me, E = COOMe
R = Ph, E = COOMe

15

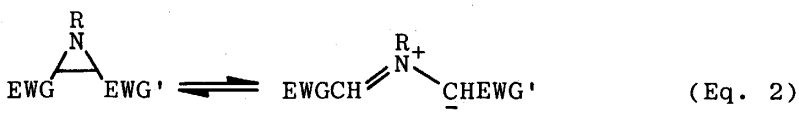


16

17

R = 2-pyridyl, R' = H
R = 1-Naph, R' = H
R = t-Bu, R' = H
R = R' = Ph

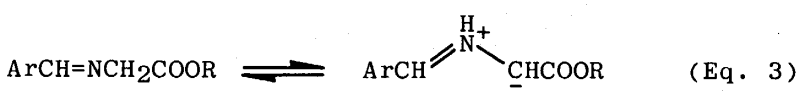
Scheme 4



(Eq. 2)

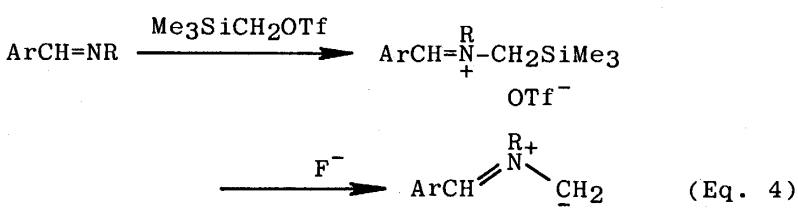
stabilized ylide

EWG: electron-withdrawing substituent



(Eq. 3)

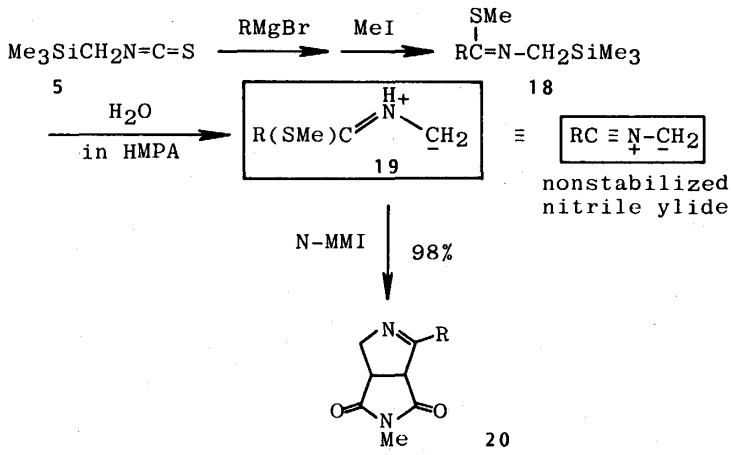
imine-azomethine ylide tautomerism



(Eq. 4)

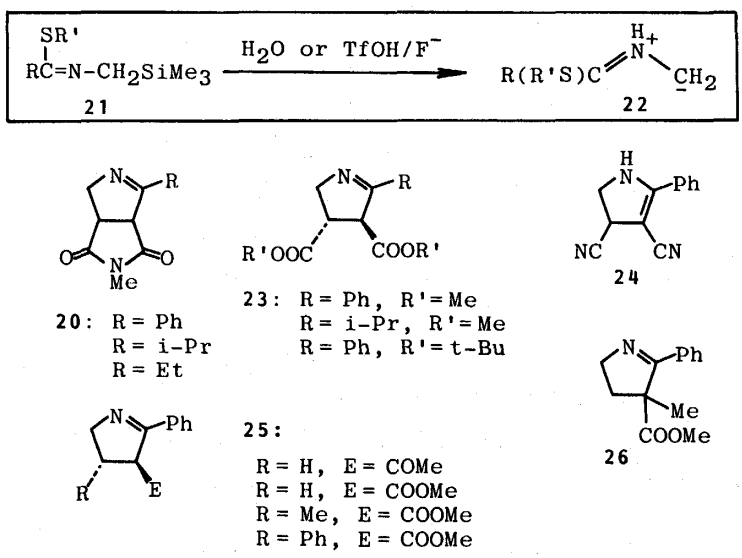
N-(Trimethylsilyl)methyl thioimidates **18** are readily available from (trimethylsilyl)-methyl isothiocyanate (**5**) via the reactions with organometallics followed by *S*-methylation with methyl iodide (Scheme 5).[15] Treating thioimidates **18** with water should generate the corresponding azomethine ylides **19.** As a result, a sequence of water-induced generation of azomethine ylides, cycloadditions with *N*-methylmaleimide as an olefinic dipolarophile, and spontaneous elimination of methanethiol gives rise to 1-pyrrolines **20,** indicating the equivalency of *N*-silylmethyl thioimidates **18** as nitrile ylide synthons of the nonstabilized types.

A variety of thioimidate ylides **22** bearing a phenyl or an alkyl substituent can be generated



Scheme 5

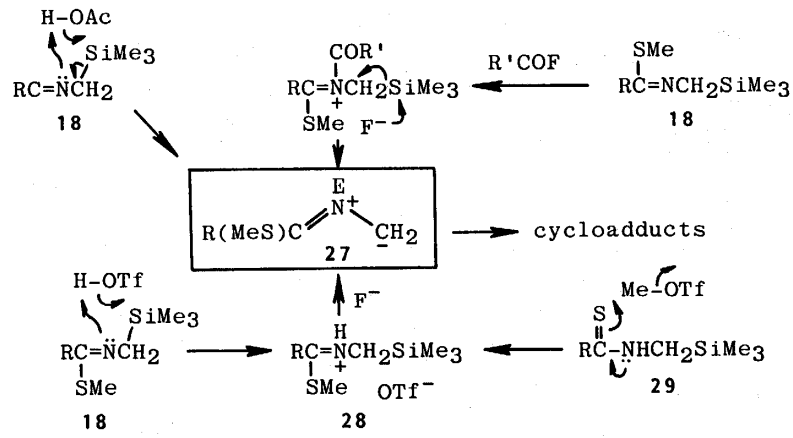
from thioimidates **21** by a similar method. The ylides **22** (R=Ph) with a phenyl substituent revealed high reactivity toward olefinic dipolarophiles to give 1-or 2-pyrrolines **20** and **23–26,** while alkylsubstituted ylides **22** (R=*i*-Pr or Et) reacted only with highly activated olefins such as maleimides or fumarates (Scheme 6). [16]



Scheme 6

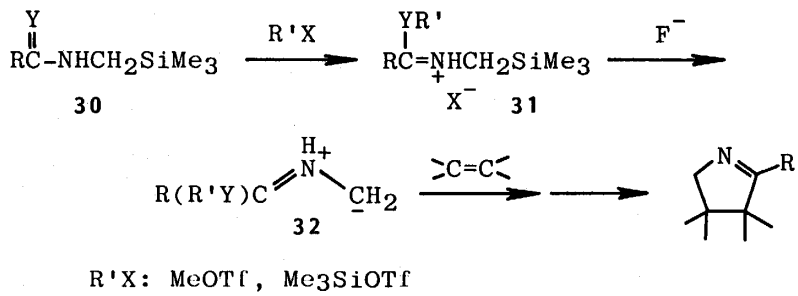
Not only water but also acetic acid and acyl fluoride serve as effective desilylating agents (Scheme 7, **18**→**27**). When trifluoromethanesulfonic acid is utilized, the corresponding iminium triflates **28** must have been formed in the reaction mixture as stable intermediates. They underwent desilylation on treatment with fluoride ion, indicating the possibility of ylide generation from the reaction of *N*-silylmethyl thioamides **29** with methyl triflate.

This possibility was actually realized by the reactions of *N*-(trimethylsilyl)methyl amidines with methyl or trimethylsilyl triflate in acetonitrile at room temperature. [17] Thus *N*-silyl-



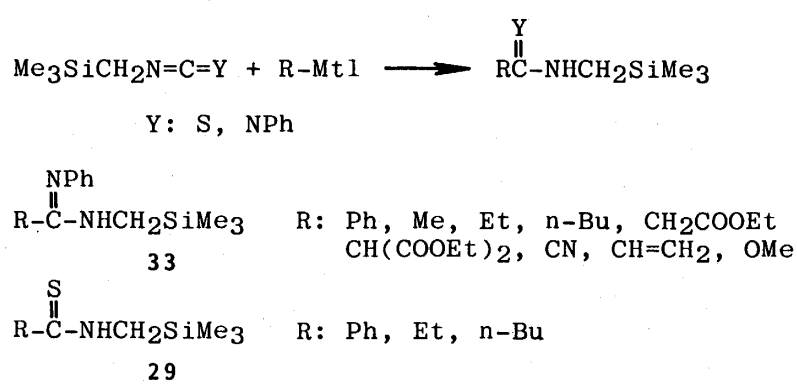
Scheme 7

methyl amidines **30** (Y=NPh) were *N'*-methylated or *N'*-silylated to form the corresponding amidinium salt precursors **31** (Y=NPh) which were subsequently desilylated by action of cesium fluoride to generate amino-substituted azomethine ylides **32** (Y=NPh) (Scheme 8). *N*-Silylmethyl thioamides **30** (Y=S) can be employed as well. [18]



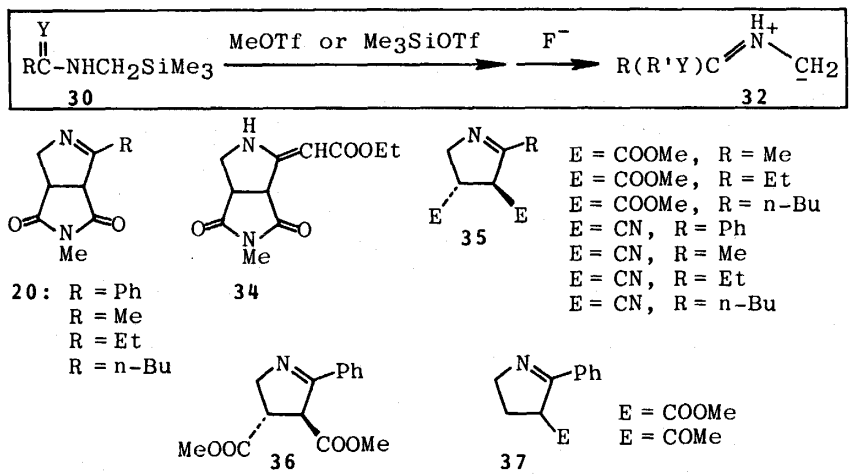
Scheme 8

A wide variety of *N*-(silylmethyl) amidines **33** and thioamides **29** were available from the reactions of *N*-[(trimethylsilyl)methyl] carbodiimide **6** and (trimethylsilyl)methyl isothiocyanate (**5**) with Grignard reagents or organolithiums, respectively (Schemes 8 and 9). [18]



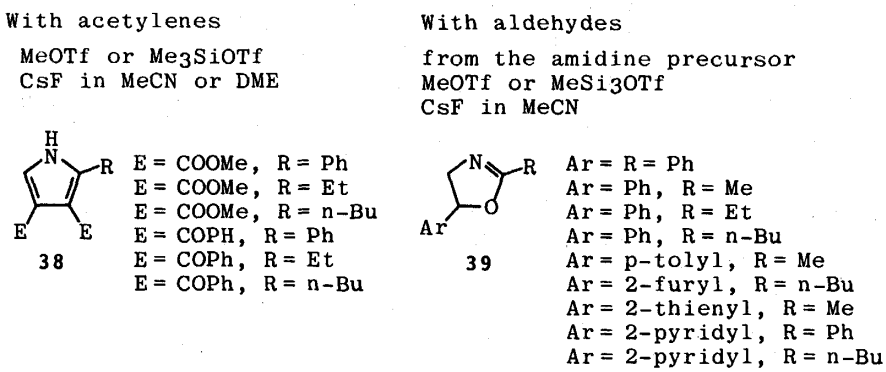
Scheme 9

Anilino- or methylthio-substitttuted azomethine ylides **32** thus generated in situ showed high reactivity toward electron-deficient olefins, acetylenes, and aromatic aldehydes enough to produce pyrrolines **20** and **34–37**, pyrroles **38**, and 2-oxazolines **39**, respectively (Schemes 10 and 11).[18] Relatively enhanced reactivity of the alkyl-substituted azomethine ylides **32** (R=alkyl) generated by this method suggests that reactivity of ylides **32** is apparently dependent upon the generation method (Scheme 6 vs Schemes 10 and 11).



Solvent: MeCN or DME. Fluoride: CsF or TBAF

Scheme 10

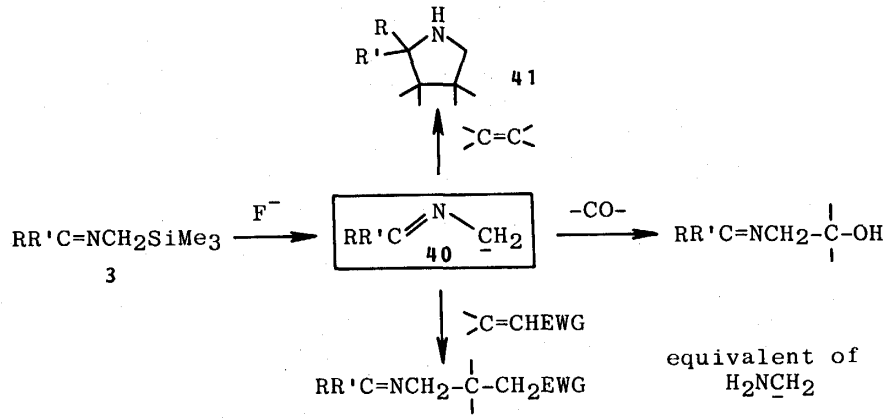


Scheme 11

2. 2-Azaallyl Anions by Desilylation Route

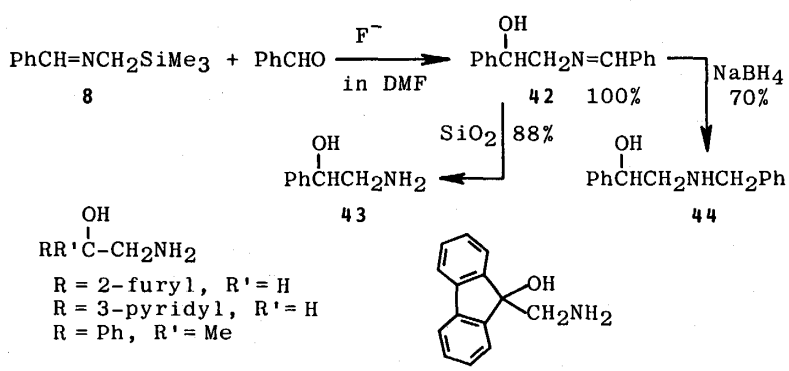
Desilylation of *N*-silylmethyl imines **3** without quaterization on the nitrogen should lead to 2-azaallyl anions **40** which can be complementary to azomethine ylides in organic synthesis. Thus *N*-benzylidene[(trimethylsilyl)methyl]amine (**8**) was desilylated with cesium fluoride in HMPA and the resulting 2-azaallyl anion **40** (R=Ph, R'=H) was captured as cycloadducts **41** with aryl-substituted olefins such as styrene, *cis*-, and *trans*-stilbenes to give the corresponding

pyrrolidines (Scheme 12).[11] As these aryl-substituted olefins are totally inactive to the azomethine ylide **10** generated from the same imine **8**, the water-induced desilylation of *N*-silylmethyl imines leading to azomethine ylides and the direct desilylation leading to 2-azaallyl anions are both of synthetic utility.



Scheme 12

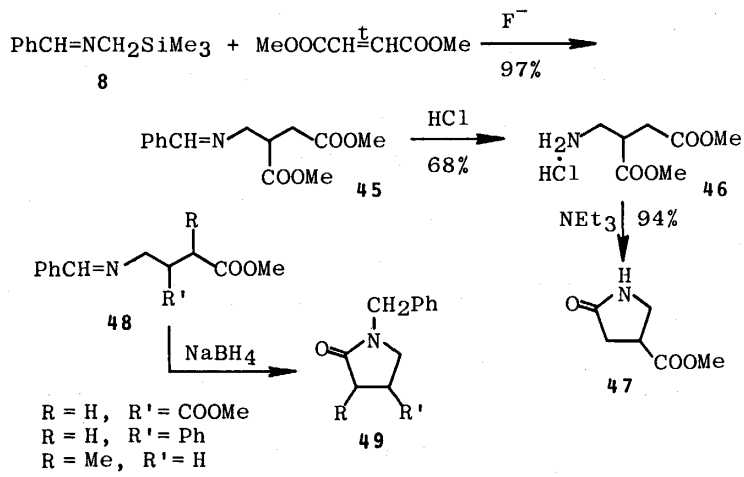
Via trappings with carbonyl compounds or Michael acceptors, theses 2-azzallyl anions **40** can be utilized as a synthetic equivalent of aminomethyl carbanion (Scheme 12). Thus the *N*-silylmethyl imine **8** was desilylated with cesium fluoride in DMF at room temperature in the presence of benzaldehyde to give 2-(benzylideneamino)-1-phenylethanol (**42**) in a quantitative yield, which was easily hydrolyzed on its column chromatography to produce 2-amino-1-phenylethanol (**43**) (Scheme 13).[11] When the carbon-nitrogen double bond of adduct **42** was reduced with sodium borohydride, the *N*-benzylated derivative **44** was obtained. Trappings can be performed with other aromatic aldehydes as well as ketones.



Scheme 13

In marked contrast with the fact that the azomethine ylides generated from *N*-silylmethyl imines **3** underwent cycloadditions with electron-deficient olefins as shown in Scheme 4, the reaction observed with 2-azaallyl anions **40** was Michael addition. For example, imine **8** was

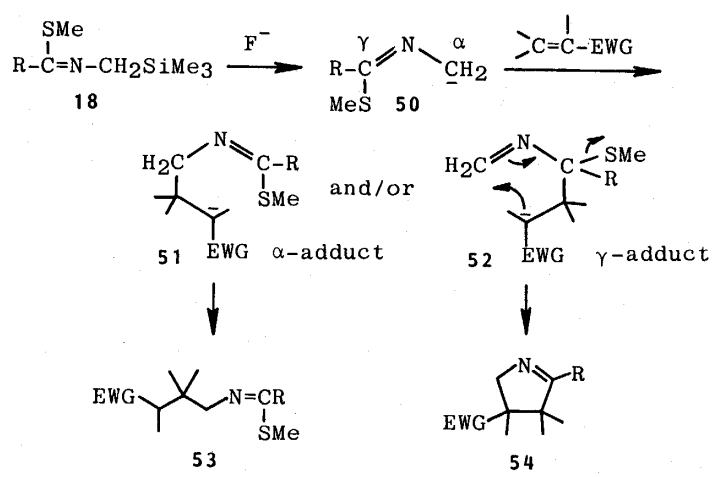
allowed to react with dimethyl fumarate in DMF in the presence of TBAF–H_2O to furnish the Michael adduct **45** in a quantitative yield (Scheme 14). Its hydrolysis into amine diester **46** and subsequent cyclization gave methyl 2-pyrrolidinone-4-carboxylate (**47**). Sodium borohydride reduction of the carbon-nitrogen double bond of similar adducts **48** afforded 1-benzyl-2-pyrrolidinones **49**.[11]



Scheme 14

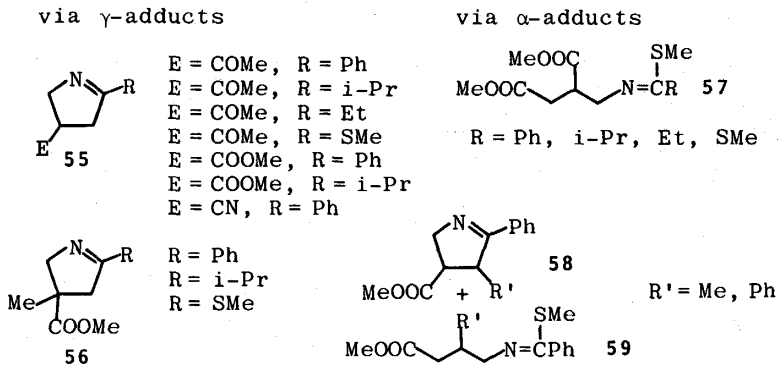
When *N*-silylmethyl thioimidates **18** are directly desilylated with fluoride ion, the methylthio-stabilized 2-azaallyl anions **50** are generated (Scheme 15). These anions **50** are sterically more crowded at the γ-position but carbanion is also more stabilized at this position. In other words, the sterically less hindered α-position has no anion-stabilizing substituent. Accordingly the regioselectivity in the Michael additions using these 2-azaallyl anions **50** should depend upon the steric size of the β-carbon of Michael acceptors.

Michael acceptors with a terminal olefinic bond such as 3-buten-2-one, methyl acrylate,



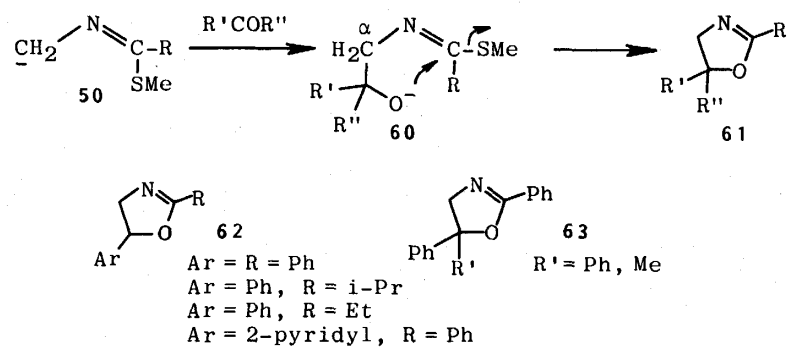
Scheme 15

acrylonitrile, and methyl methacrylate reacted with **50** at the more crowded γ-position leading to 1-pyrrolines **55** and **56** after subsequent cyclization and elimination (Schemes 15 and 16).[16] On the other hand, **50** reacted with dimethyl fumarate as an olefin bearing a more hindered reaction site at the less hindered α-position. As further cyclization is inhibited sterically, the products isolated were the Michael type adducts **57**. In the reactions with methyl crotonate or cinnamate, both **58** and **59** were produced.



Scheme 16

Carbanions **50** undergo regioselective additions to carbonyl compounds at the less hindered α-position (Scheme 17).[16] The resulting adducts **60** can cyclize readily to produce **61** via subsequent elimination of methanethiol. 2-Oxazolines **62** and **63** were synthesized by this sequence.

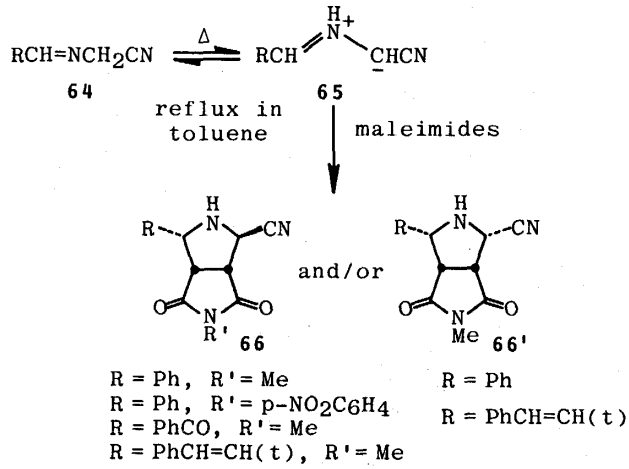


Scheme 17

3. Nitrile Ylide Equivalents from Imine-Azomethine Ylide Tautomerism

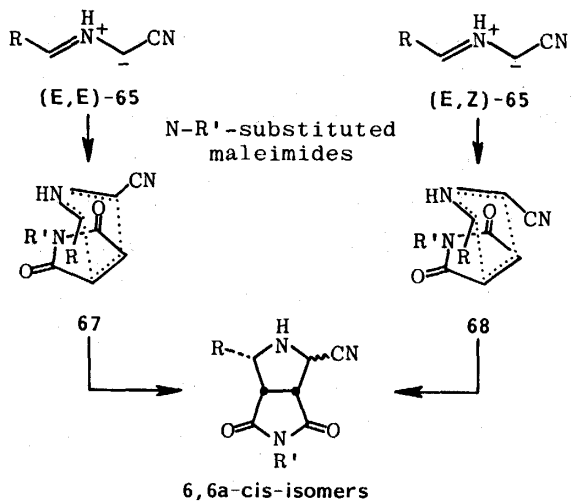
Based on the principle of imine-azomethine ylide tautomerism of imine esters,[13] imine nitriles **64** were also expected to be a precursor for cyano-stabilized azomethine ylides. Through a sequence of cycloaddition and subsequent elimination of HCN, **64** could be a synthetic equivalent of nonstabilized nitrile ylides. Thus heating imines **64** of aminoacetonitrile under reflux in toluene generated *N*-unsubstituted azomethine ylides **65** of the cyano-stabilized type which were

trapped with *N*-methylmaleimide to give two stereoisomeric 6,6a-*cis*-cycloadducts **66** and **66'** (Scheme 18).[19]



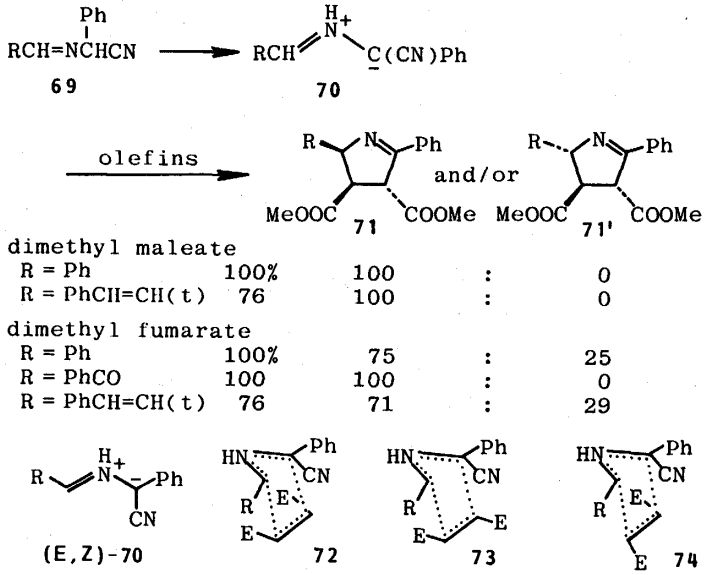
Scheme 18

There are two stereoisomers (*E*, *E*)−**65** and (*E*, *Z*)−**65** possible with almost equal stability for the intermediary azomethine ylides **65** (Scheme 19). Endo cycloaddition reactions of these ylide isomers via approaches **67** and **68** should lead to 6,6a-*cis*-cycloadducts **66** and **66'**. These are the case observed.[19]



Scheme 19

The imines **69** of α-aminophenylacetonitrile similarly generate azomethine ylides **70** which give rise to 1-pyrrolines in cycloadditions with olefins. Since the most stable ylide configuration of **70** must be E,Z-isomer from the steric viewpoint, selective formation of 4,5-*cis*-1-pyrrolines **71** from the reactions with dimethyl maleate is via the endo approach **72** (Scheme 20).[20] Such high endo selection is presumably attributable to the attractive interactions working



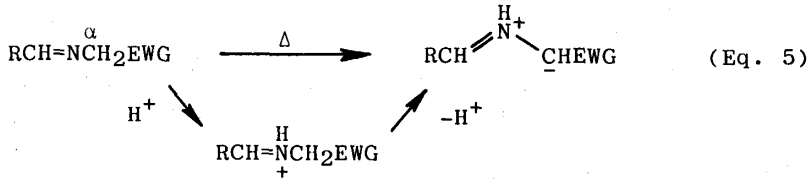
Scheme 20

between the phenyl and the ester and between the R and the ester. On the other hand, similar reactions of ylides **70** with dimethyl fumarate were less stereoselective. Two approaches **73** (attraction between the R and the ester) and **74** (attraction between the phenyl and the ester) are energetically comparable in this case and therefore they competed each other.

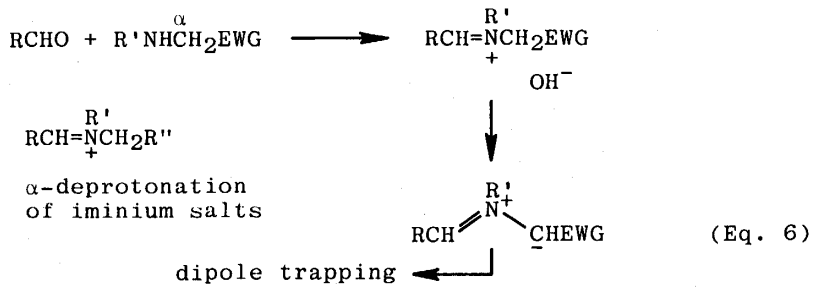
4. Ylide Generation by Deprotonation Method

Thus thermal tautomerism of the imines bearing an acidic α-hydrogen generates *N*-unsubstituted azomethine ylides. This tautomerism can be regarded as involving two steps of *N*-protonation of the imines and subsequent α-deprotonation (Equation 5). Similar iminium intermediates would be more conveniently accessible by the condensation of *N*-substituted α-amino esters with carbonyl compounds (Equation 6). Although α-deprotonation of iminium salts have not been a practical generation method of azomethine ylides,[21] this condensation would be much more realizable. This optimism comes from the expectation of rapid α-deprotonation from the intermediary salts. The counter anion is strongly basic hydroxide and in addition the α-hydrogen is highly acidic.

According to Equation 6, *N*-substituted α-amino esters and aldehydes were heated under reflux in toluene with continuous removal of water generating the expected azomethine ylides **75**

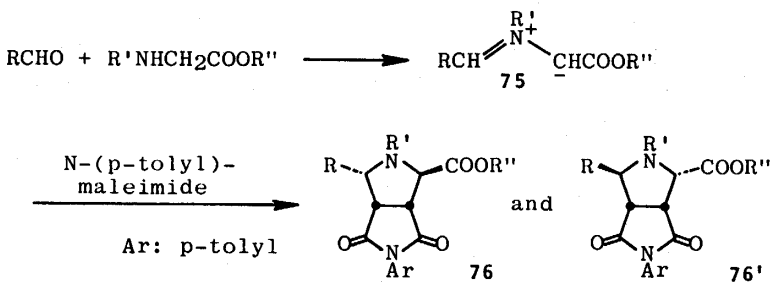


(Eq. 5)



(Eq. 6)

of ester-stabilized types (Scheme 21).[22] The ylides **75** were trapped with *N*-(*p*-tolyl)maleimide to furnish two stereoisomers of cycloadducts **76** and **76′**. The assigned stereostructures of **76** and **76′** show the selective participation of *anti*-**75** in the cycloadditions; the endo/exo selectivity depends not upon the substituent R from carbonyl compounds but upon the steric size of the *N*-substituent.[23]



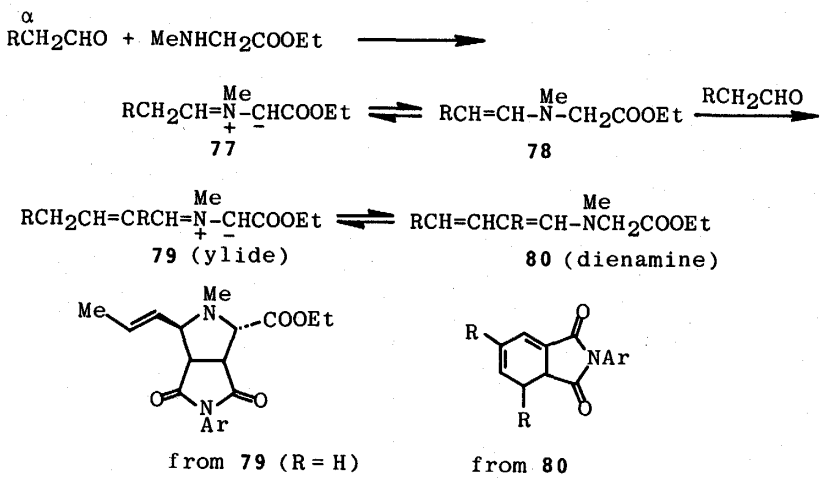
RCHO	R'	R"	yield	endo	:	exo
PhCHO	Me	Et	93%	78	:	22
EtCHO	Me	Et	66	77	:	23
MeCHO	Me	Et	87*	76	:	24
HCHO	Me	Et	93	62	:	38
PhCHO	Ph	Me	77	45	:	55
EtCHO	Ph	Me	64	47	:	53
HCHO	Ph	Me	78	50	:	50

* R = MeCH=CH(t)

Scheme 21

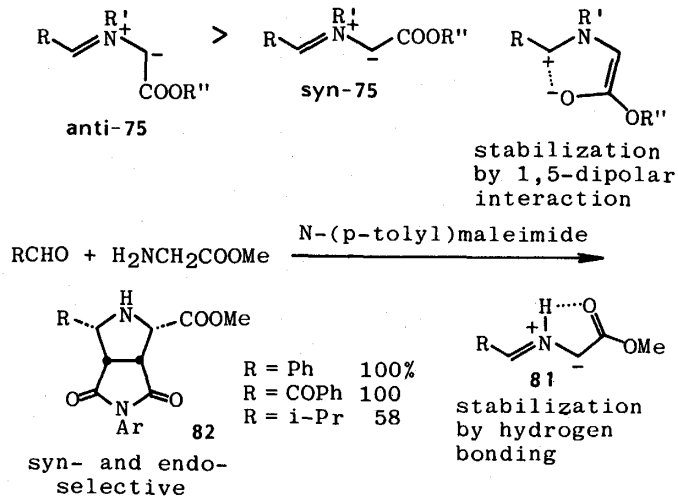
When an aliphatic aldehyde is employed in the above ylide generation, the resultant azomethine ylide **77** enters into an equilibration with enamine **78** so that the second molecule of the aldehyde can undergo condensation with **78** leading to 1-alkenyl-substituted azomethine ylide **79** and further dienamine **80** (Scheme 22). The products isolated were the cycloadducts of **79** and/or **80** with the maleimide.[24]

The selective participation of *anti*-**75** makes a striking contrast to the exclusively syn-selective cycloadditions of *N*-unsubstituted azomethine ylides **81** of the ester-stabilized types (Scheme 23). Ylides **81** could be similarly generated from primary amino esters and aldehydes, and underwent exclusively *endo*-selective cycloadditions with a maleimide to give **82.**[24] Relatively high stability of *anti*-**75** may be due to the stabilization by proximate interaction of the extended 1,5-dipolar form as already discussed before in the cases of heteroaromatic *N*-



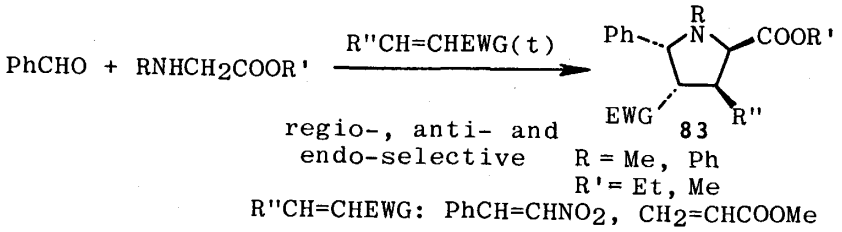
Scheme 22

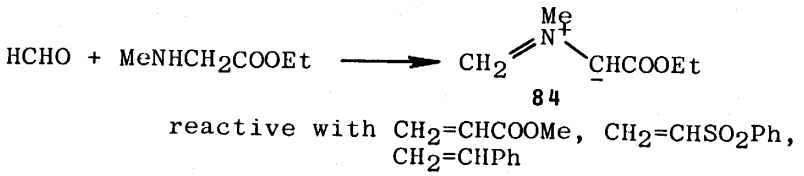
ylides.[25] On the other hand, ylide **81** is stabilized in a *syn*-form due to the stabilization by hydrogen bonding.



Scheme 23

When (*E*)-β-nitrostyrene or methyl acrylate was employed instead of *N*-(*p*-tolyl)maleimide, the cycloadditions with *anti*-**75** (R=Ph) were completely regio-, *anti*-, and *endo*-selective to provide cycloadducts **83** (Scheme 24).[24] Condensation between paraformaldehyde and an *N*-substituted amino ester generates the azomethine ylide **84** with an ester as the only *C*-substituent.

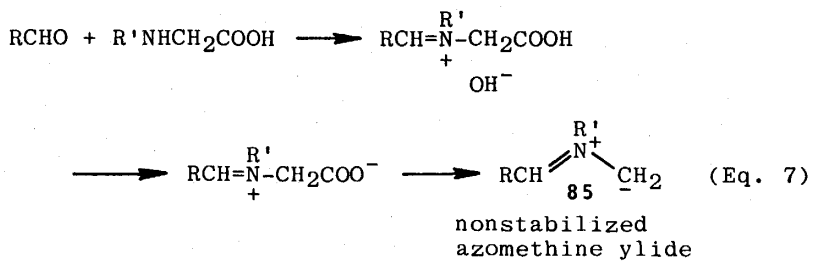




Scheme 24

5. Ylide Generation by Decarboxylative Condensation

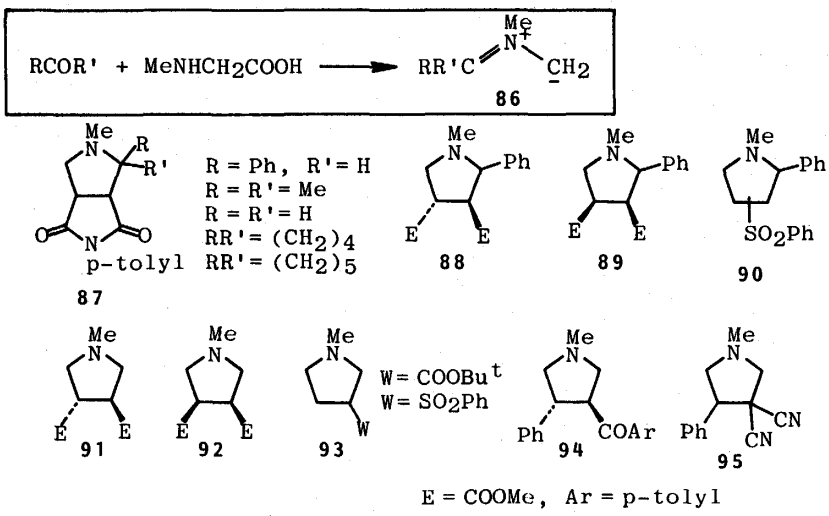
Use of α-amino acids instead of the α-amino esters in Equation 6 would offer a new generation method of azomethine ylides. Condensations between *N*-substituted α-amino acids and carbonyl compounds would lead to iminium hydroxides which then spontaneously lose a proton to give iminium carboxylate betaines. Decarboxylation from the betaine intermediates generates azomethine ylides **85** of the nonstabilized types (Equation 7). [26]



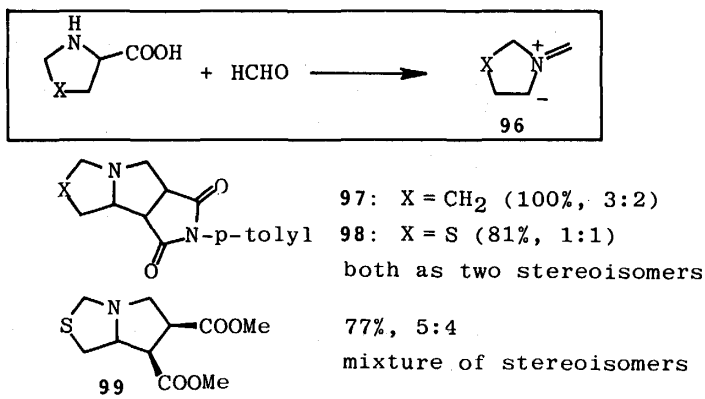
According to this plan (Equation 7), sarcosine was heated under reflux in toluene with a variety of carbonyl compounds such as benzaldehyde, acetone, paraformaldehyde, cyclopentanone, and cyclohexanone. The resulting azomethine ylides **86** were trapped with a variety of olefins to give excellent yields of cycloadducts **87–95** (Scheme 25). [27] The condensation with paraformaldehyde is a convenient generation method of *C*-unsubstituted azomethine ylides **86** (R=R'=H).

Condensations of cyclic α-amino acids such as proline and thiazolidine-4-carboxylic acid with paraformaldehyde generate azomethine ylides **96** carrying a fused heterocycle (X=CH_2 or S). Their cycloadditions with *N*-(*p*-tolyl)maleimide and dimethyl maleate give **97**, **98**, and **99**, all as mixtures of two stereoisomers (Scheme 26). *Endo*-selectivity of these cycloadditions were poor. [27]

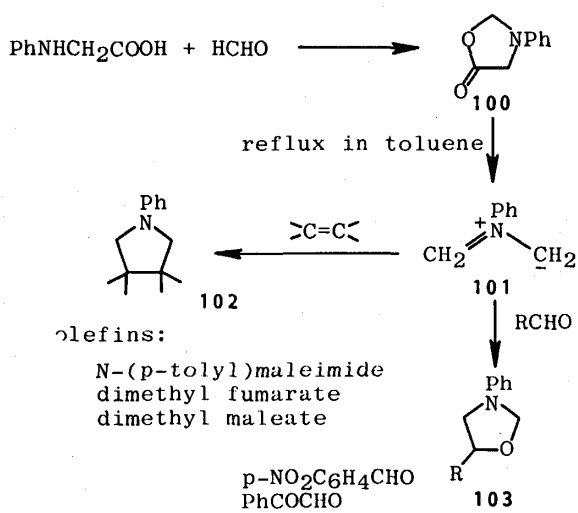
Interestingly the reactin of *N*-phenylglycine with paraformaldehyde under reflux in toluene



Scheme 25



Scheme 26

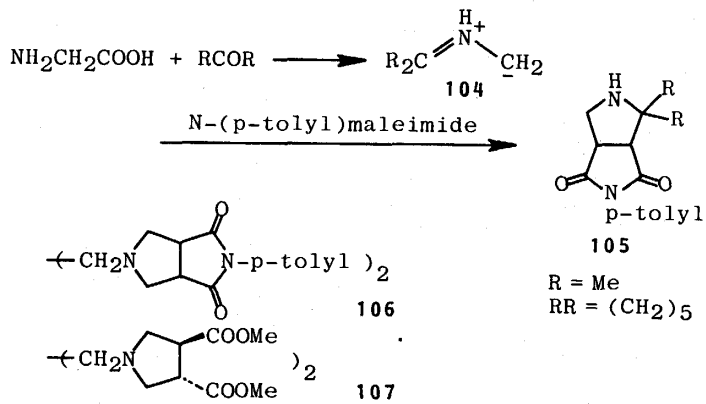


Scheme 27

produced 3-phenyl-5-oxazolidinone (**100**) as a stable product (Scheme 27). Heating the isolated **100** in toluene caused decarboxylation to generate azomethine ylide **101** which was trapped with

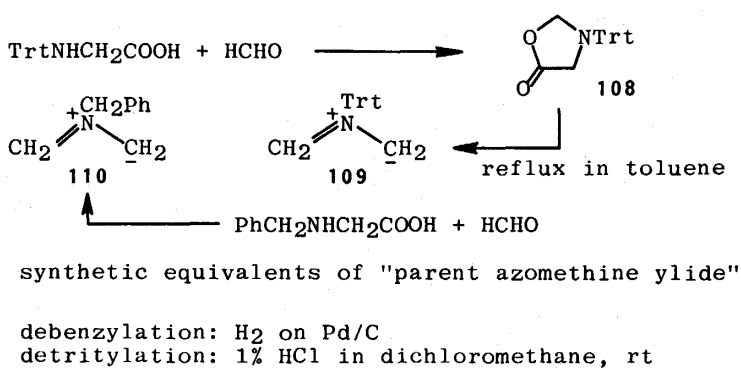
several dipolarophiles to give cycloadducts **102**, indicating that 5-oxazolidinone **100** is the precursor of azomethine ylide **101**.[27] Successful isolation of the precursor **100** enabled cycloadditions of nonstabilized azomethine ylides with carbonyl compounds: Thus ylide **101** was trapped with highly activated aldehydes such as *p*-nitrobenzaldehyde and phenylglyoxal.

Ylide generation by the decarboxylation route can utilize *N*-unsubstituted α-amino acid, glycine. Although the condensations with acetone or cyclohexanone provided the corresponding *N*-unsubstituted azomethine ylides **104** which were trapped with *N*-(*p*-tolyl)maleimide as cycloadducts **105**, all attempts to generate the parent ylide **104** (R=H) were unsuccessful (Scheme 28). The products isolated in the reactions with the maleimide or dimethyl fumarate are **106** and **107**, which were presumably produced via the cycloadducts of the parent azomethine ylides.



Scheme 28

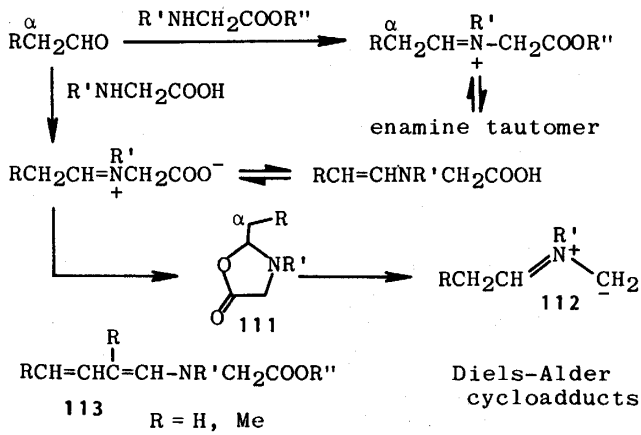
The decarboxylation route using *N*-protected glycines and paraformaldehyde would lead to the synthetic equivalents of parent azomethine ylide **104** (R=H). Thus, *N*-tritylglycine or *N*-benzylglycine was allowed to react with paraformaldehyde.[27] In the former reaction, 3-trityl-5-oxazolidinone (**108**) was quantitatively isolated as a stable product; heating **108** under reflux in toluene generated azomethine ylide **109** which was trapped with several olefinic dipolarophiles (Scheme 29). On the other hand, the condensation with *N*-benzylglycine directly generated ylide



Scheme 29

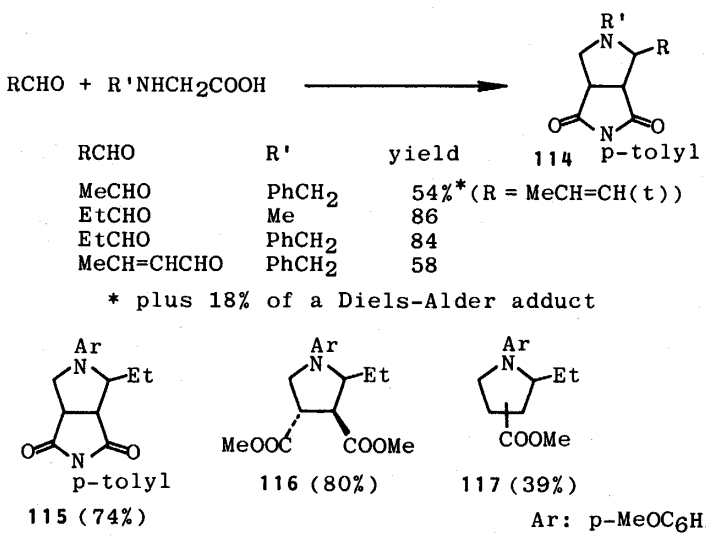
110. Deprotection from the cycloadducts was carried out with 1% aqueous HCl in dichloromethane at room temperature for the cycloadducts of **109** or with catalytic tydrogenation on Pd/C for the ones of **110.**

One disadvantage of the deprotonation route shown in Equation 6 is ready transformation of the iminium intermediates formed from aliphatic aldehydes into enamine tautomers (Scheme 22). In the decarboxylative generation, the intermediary iminium salts are expected to be deprotonated rapidly at the carboxyl moiety rather than the α-position and undergo cyclization into 5-oxazolidinones **111** (Scheme 30). Therefore, the further condensation leading to dienamine **113** as a side reaction in the deprotonation route would be inhibited.



Scheme 30

Reactions of *N*-substituted α-amino acids with a variety of aldehydes were carried out and the resulting azomethine ylides were trapped with *N*-(*p*-tolyl)maleimide to give cycloadducts **114** (Scheme 31). The condensation with propanal showed no sign of formation of dienamines

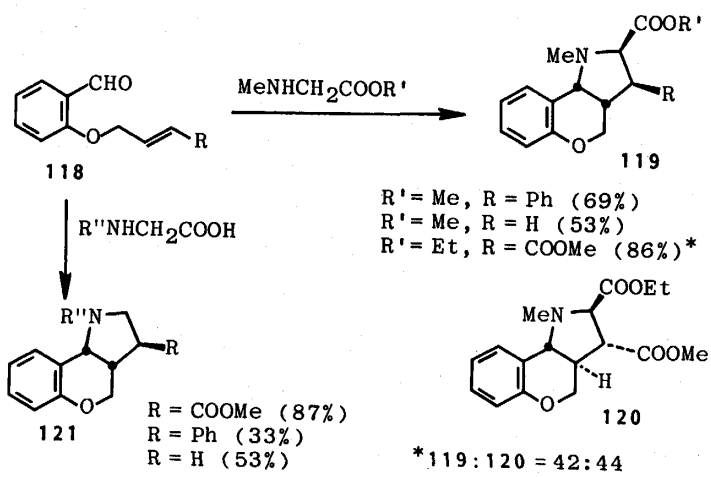


Scheme 31

as expected, **114** (R=Et) being the only product. The closely related alkyl-substituted ylide underwent smooth cycloadditions with *N*-(*p*-tolyl)maleimide, dimethyl fumarate, and methyl acrylate to give **115–117.** However, the reaction with acetaldehyde generated not the methyl-substituted ylide **112** (R=H) but 1-propenyl-substituted ylide, showing the formation of enamine intermediate. It is therefore concluded that aliphatic aldehydes other than acetaldehyde can be successfully applied to the generation of azomethine ylides by the decarboxylation route. [28]

6. Intramolecular Cycloadditions

Both the deprotonation and decarboxylation routes are especially useful for the ylide generation in interamolecular trapping reactions, since ylides can be in situ generated by simple heating of α-amino esters or acids with the carbonyl compounds bearing an internal dipolarophile. Thus aldehydes **118** were heated under reflux in toluene with sarcosine esters (Scheme 32). The resulting ylides were intramolecularly trapped to give fused pyrrolidines **119.** [28] From *o*-(cinnamyloxy)- and *o*-(allyloxy)benzaldehydes **118** (R=Ph and H) *cis*-fused cycloadducts **119** were exclusively produced, while a 42:44 mixture of *cis*- and *trans*-fused cycloadducts **119+120** was obtained from the aldehyde **118** bearing an ester-activated olefin moiety. The comparable formation of **120** may be bue to steric repulsion between the two ester groups in the *cis*-approach. On the other hand, decarboxylative condensations of **118** with *N*-substituted α-amino acids selectively furnished *cis*-fused pyrrolidines **121.**

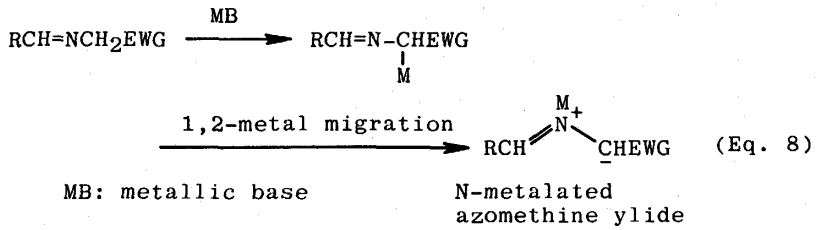


Scheme 32

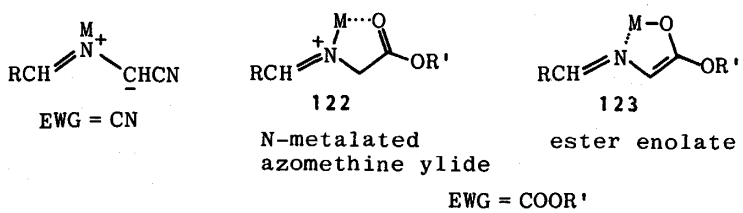
7. *N*-Metalated Azomethine Ylides

As already mentioned in Equation 5, the α-hydrogen of imine esters and nitriles is so acidic that it thermally migrates to the adjacent nitrogen generating *N*-protonated (or *N*-unsubstitu-

ted) azomethine ylides. The concept of imine-azomethine ylide tautomerism can be extended to a new type of azomethine ylides according to the process shown in Equation 8.

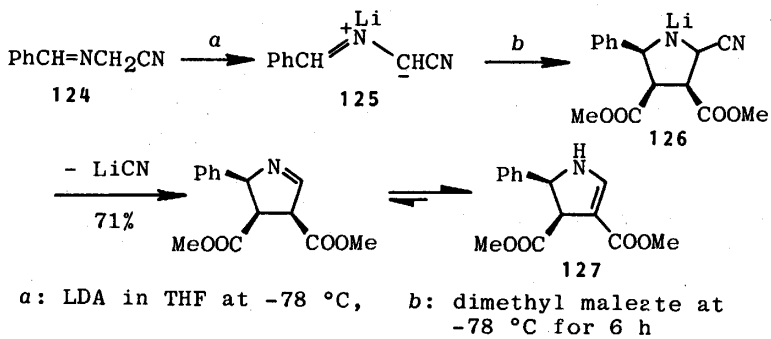


α-Metalation of the imines activated by an electron-withdrawing substituent forms a *C*-metalated intermediate which undergoes spontaneous 1,2-metal migration, from carbon to nitrogen, leading to *N*-metalated azomethine ylides. The *N*-methalated azomethine ylides **122** derived from imine esters are tautomeric isomers of metal ester enolates **123** (Scheme 33).



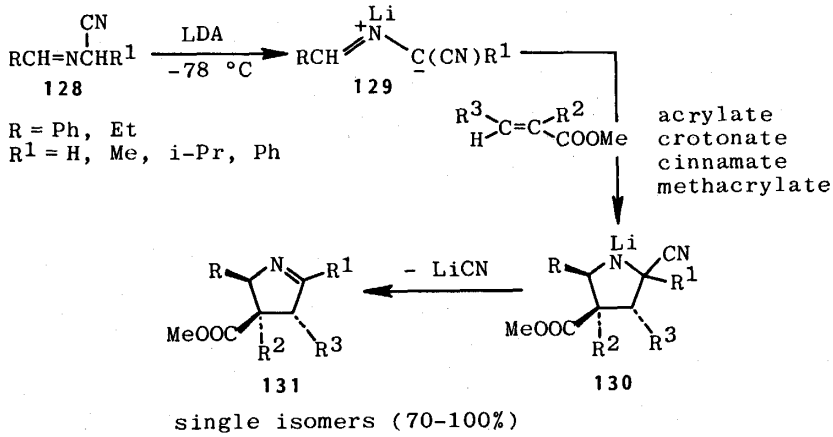
Scheme 33

When (benzylideneamino)acetonitrile (**124**) was treated with LDA in THF at −78°C for 5 min, a red colored solution, probably the color of *N*-lithiated azomethine ylide **125**, was formed. This ylide **125** was trapped with dimethyl maleate at the same temperature to give 4,5-*cis*-2-pyrroline-3,4-dicarboxylate **127** in 71% yield as single isomer (Scheme 34).[29] This reaction includes *endo*-selective and *cis*-specific cycloaddition leading to cycloadduct **126**, followed elimination of LiCN, and final isomerization through an imine-enamine tautomerism.



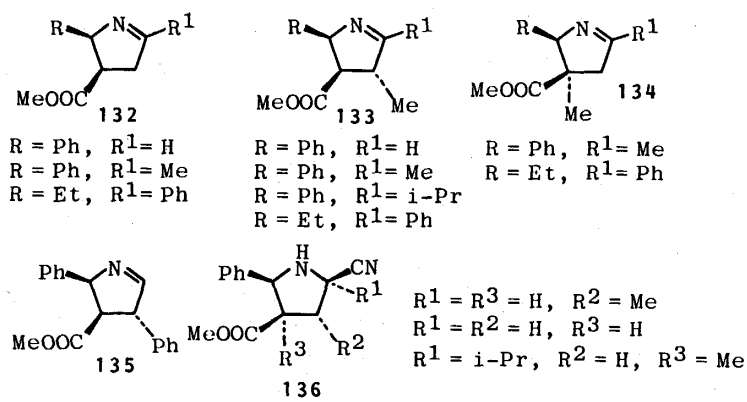
Scheme 34

A variety of α-(alkylideneamino) nitriles **128** were similarly treated with LDA at −78°C to generate *N*-lithiated azomethine ylides **129** (Scheme 35). Substituent R can be chosen among aryl and alkyl; R^1 among hydrogen, alkyl and aryl. Ylides **129** underwent smooth cycloadditions to unsymmetrical olefins such as methyl acrylate, crotonate, cinnamate and methacrylate to give l-pyrrolines **131** in 70–100% yields. In some cases cyano-remaining cycloadducts, pyrrolidines **130**, were isolated. [29]



Scheme 35

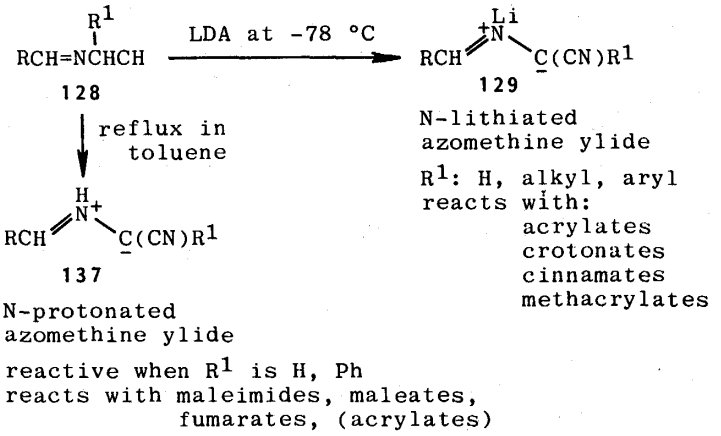
Regardless of the substitution patterns and kinds of substituents of imines **128** and olefins, all cycloadditions are exclusively regioselective, stererospecific, and stereoselective (Scheme 36). The ester moiety is adjacent and cis to the imine substituent R. Geometry of the starting olefins was retained in cycloadducts **131**. Advantages of *N*-lithiated azomethine ylides **129** over the corresponding *N*-protonated ylides are summarized in the following several schemes.



Scheme 36

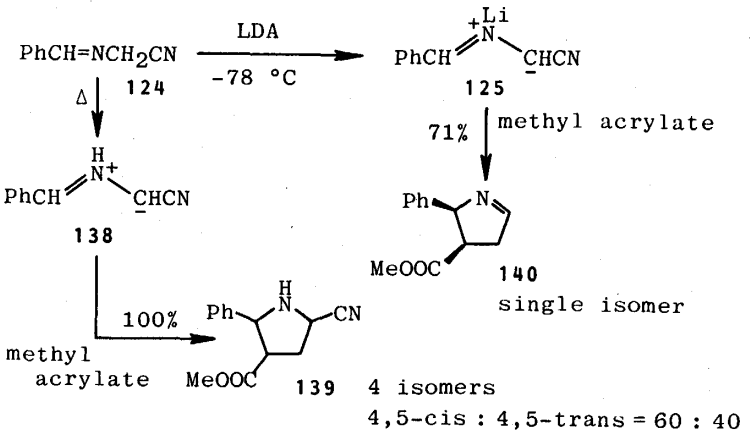
The first advantage is an enhanced reactivity. *N*-Protonated azomethine ylides **137** are generated at about 110°C and they are reactive only when R^1 is hydrogen or phenyl. [20] Ylides

137 undergo cycloadditions with such reactive olefins as maleimides, maleates, fumarates, and sometimes acrylates (Scheme 37). On the other hand, reactivity of *N*-lithiated azomethine ylides **129** does not depend upon the substituent R^1. They can react with less reactive olefins such as acrylates, crotonates, cinnamates, and methacrylates even at −78°C. [29]



Scheme 37

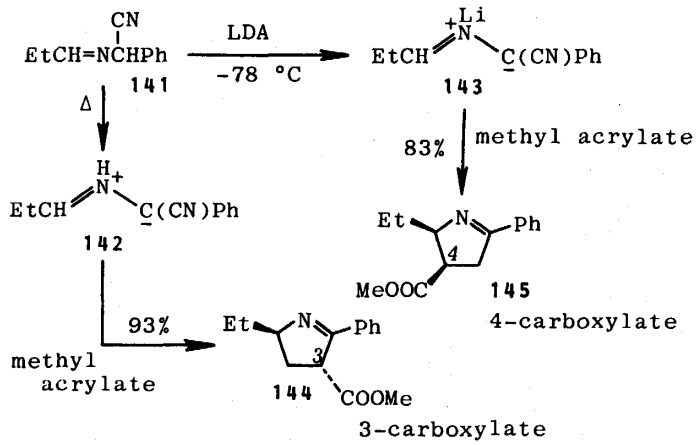
The second advantage is a high *endo*-selectivity. Cycloaddition of the *N*-protonated azomethine ylide **138** thermally generated from (benzylideneamino)acetonitrile (**124**) with methyl acrylate proceeds quantitatively, but is so poor in stereoselectivity that a mixture of four stereoisomeric pyrrolidines **139** is produced (Scheme 38). [19] On the other hand, the reaction of *N*-lithiated azomethine ylide **125** gave 4,5-*cis*-1-pyrroline-4-carboxylate **140** as a single stereoisomer (71%). [29]



Scheme 38

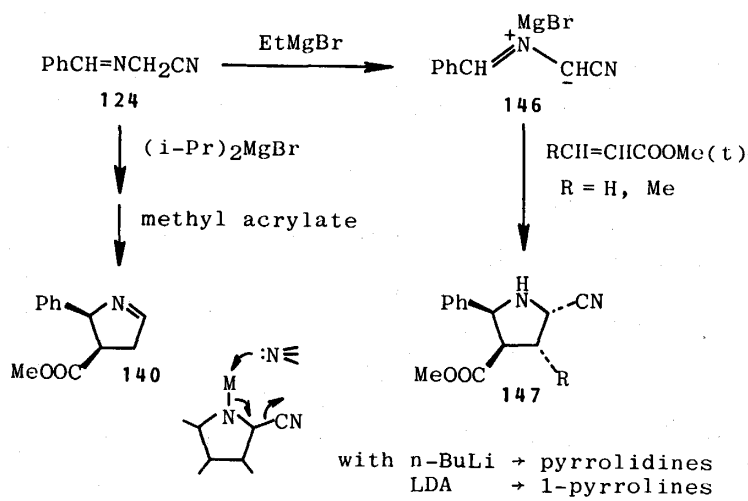
The third advantage is a high regioselectivity. The *N*-protonated azomethine ylide **142** thermally derived from imine **141** undegoes regioselective cycloaddition to methyl acrylate to give 5-ethyl-1-pyrroline-3-carboxylate **144** in 93% yield. [20] This is the regioisomer whose forma-

tion is expected on the molecular orbital basis. Interestingly the *N*-lithiated ylide **143** showed a reverse regioselectivity to furnish 5-ethyl-1-pyrroline-4-carboxylate **145** in 83% yield (Scheme 39).[29] Pyrroline **145** was known to be available by the LDA/LiI-induced cis cyclization of the Michael adduct between **141** and methyl acrylate,[30] showing that ylide **143** has somewhat carbanion-like property.



Scheme 39

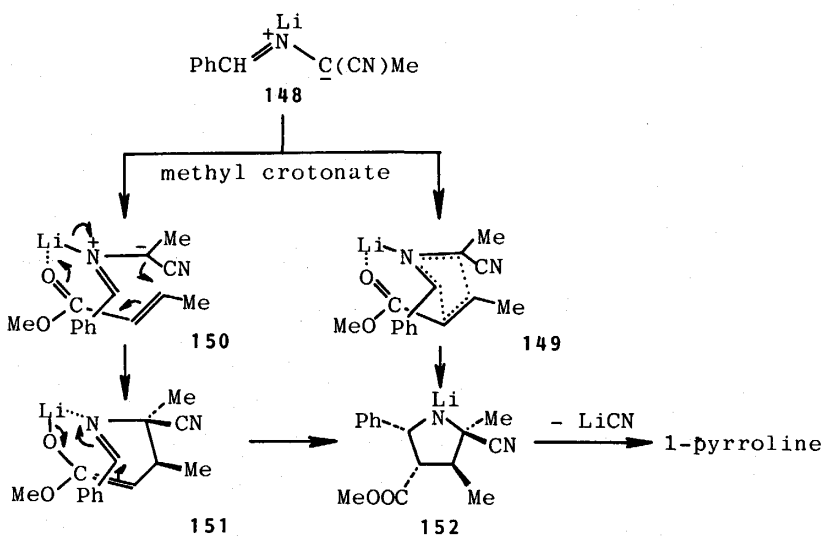
Activation of imine nitriles can be also conducted by employing metallic bases other than LDA. Ethylmagnesium bromide, magnesium diisopropylamide bromide, butyllithium, butyllithium and a lithium halide, butyllithium and triethylamine, and butyllithium and titanium (IV) isopropoxide are effective.[29] Treatment of imine nitrile **124** with ethylmagnesium bromide generated *N*-magnesio azomethine ylide **146** which was trapped with methyl acrylate or crotonate giving cyano-remaining pyrrolidines **147** as single stereoisomers (Scheme 40). On the other hand, 4,5-*cis*-1-pyrroline **140** was exclusively obtained when imine **124** was activated with



Scheme 40

magnesium diisopropylamide bromide. Similar difference was observed between butyllithium and LDA, pyrrolidines and pyrrolines being the only products, respectively. The reason would be that cleavage of the metal-nitrogen bond in the cycloadducts becomes easy if an amine is coordinating with the metal.

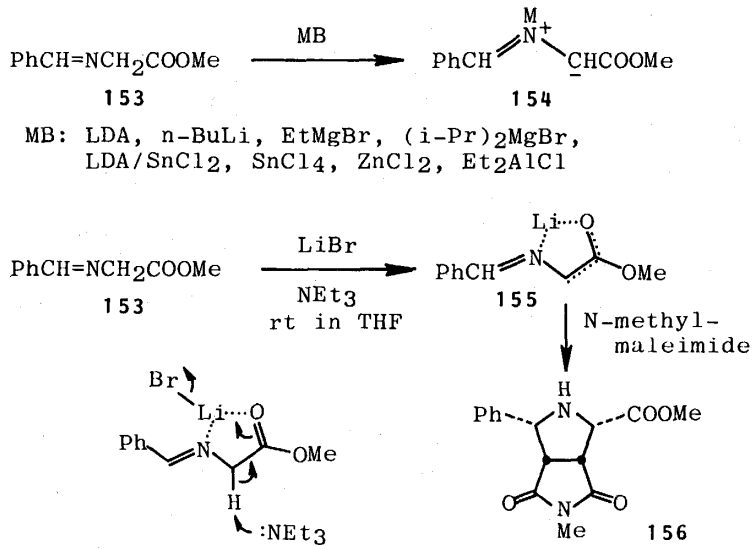
Stereochemical outcome of the cycloadditions of *N*-lithiated azomethine ylides with olefinic dipolarophiles can be explained with the metal chelation onto the ester oxygen of the olefins. Methyl-substituted ylide **148** and methyl crotonate were selected as a typical combination to show possible reaction pathways with (Scheme 41). Ylide **148** should take an *E,E*-configuration since it is sterically most stable. Coordination of the lithium metal to the carbonyl oxygen of the olefinic esters is the important stereochemistry-determing step. Either by a concerted cycloaddition (**148** → **149** → **152**) or a stepwise cyclization path (**148** → **150** → **151** → **152**), 4,5-*cis*-pyrrolidine **152** is formed as the initial cycloadduct. Elimination of lithium cyanide leads to 4,5-*cis*-1-pyrroline. The high regioselectivity would be better explained by the stepwise Michael-type cyclization, but the concerted mechanism can not be excluded.



Scheme 41

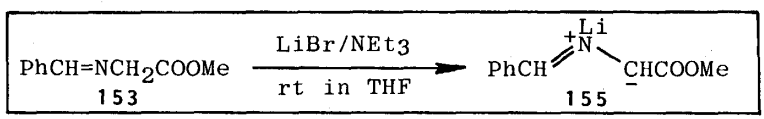
Great success in the ready generation of highly reactive *N*-metalated azomethine ylides **129** and **146** of the cyano-stabilized types encouraged us to extend our study to the generation of *N*-metalated azomethine ylides from the imines of α-amino esters. According to the method developed on imine nitriles, methyl *N*-(benzylideneamino)glycinate (**153**) was treated, at −78°C in THF, with a variety of metallic bases such as LDA, butyllithium, ethylmagnesium bromide, and magnesium diisopropylamide bromide. Combinations of butyllithium and several Lewis acids such as tin(II) chloride, tin(IV) chloride, zinc(II) chloride, and diethylaluminum chloride were also employed (Scheme 42). But no evidence for the generation of *N*-metalated azomethine ylides **154** was obtained. In most cases the olefins employed to trap the generated ylides

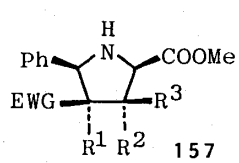
were recovered as polymeric forms, indicating that use of a weaker base is needed for the activation of **153**. After screening of a variety of bases, imine ester **153** was treated with lithium bromide (1.5 equiv) plus triethylamine (1.3 equiv) in THF at room temperature. The resulting anionic species **155**, either *N*-lithiated azomethine ylide **122** (R=Ph, R^1=Me, M=Li) or lithium ester enolate **123** in Scheme 33, was captured by *N*-methylmaleimide to give all-cis cycloadduct **156** as a single isomer in 83% yield (Scheme 42).[31] Lithium bromide acitivates imine **153** by coordinating to the carbonyl oxygen ant to the imine nitrogen. Thus the activated acidic α-hydrogen can be deprotonated with such a weak base as triethylamine.



Scheme 42

Ylide **155** similarly reacted with a variety of carbonyl-activated olefins such as dimethyl maleate, fumarate, methyl acrylate, crotonate, methacrylate, 3-buten-2-one, (*E*)-3-penten-2-one, (*E*)-4-phenyl-3-buten-2-one, and (*E*)-3-oxo-1-phenyl-3-(*p*-tolyl)propene to give single isomers of cycloadducts **157** in excellent yields (Scheme 43).[31] Thus the cycloadditions of **155** are abso-





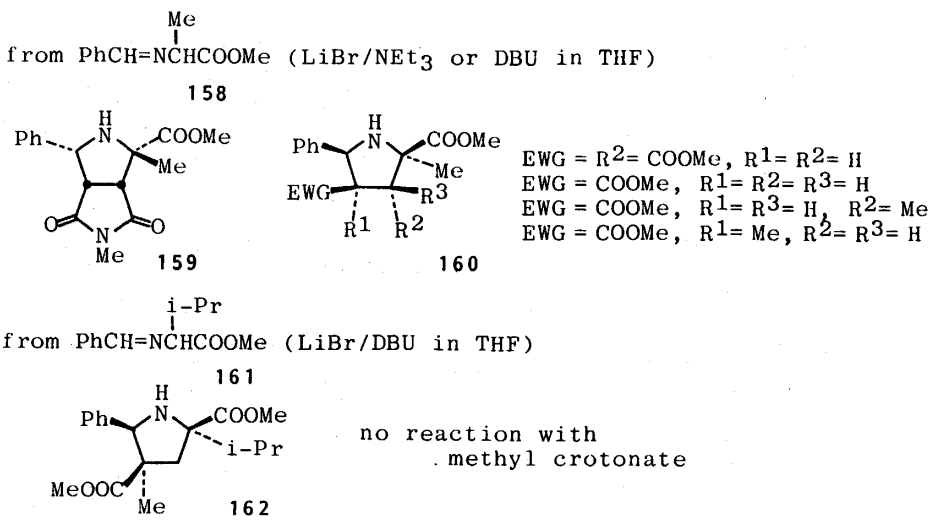
all single isomers

EWG = R^3= COOMe, R^1= R^2= H
EWG = R^2= COOMe, R^1= R^3= H
EWG = COOMe, R^1= R^2= R^3= H
EWG = COOBu-t, R^1= R^2= R^3= H
EWG = COOMe, R^1= R^3= H, R^2= Me
EWG = COOMe, R^1= R^3= H, R^2= Ph
EWG = COOMe, R^1= Me, R^2= R^3= H
EWG = COMe, R^1= R^2= R^3= H
EWG = COMe, R^1= R^3= H, R^2= Me
EWG = COMe, R^1= R^3= H, R^2= Ph
EWG = CO-p-tolyl, R^1= R^3= H, R^2= Ph

Scheme 43

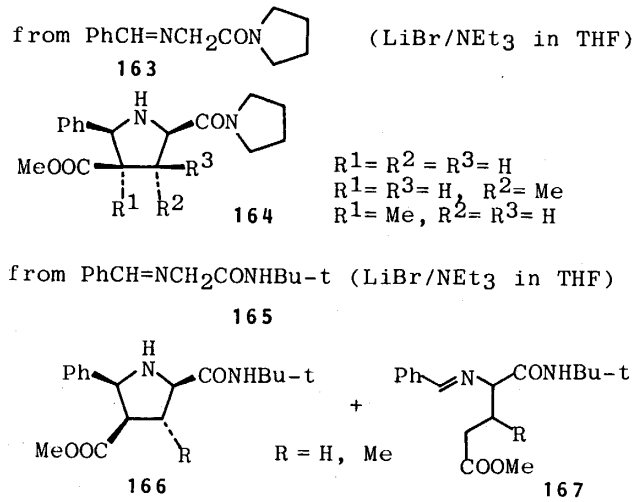
lutely regioselective, *cis*-selective with respect to the ylide, *endo*-selective between Ph and carbonyl moieties, and exclusively stereospecific with respect to the olefins. The *N*-lithiated azomethine ylide **155** is stabilized by a chelation to the carbonyl carbon so that the phenyl and the ester are syn to each other. In other words, *N*-lithio azomethine ylide **155** of the ester-stabilized type has *E,E*-geometry.

When an alkyl group is introduced to the α-position of *N*-(benzylidene)glycinate **153**, α-deprotonation with triethylamine became sluggish because of steric hindrance. This difficulty was dissolved by use of DBU as a stronger base. Although these α-alkylated *N*-lithio azomethine ylides still showed high diastereoselectivity as well, their reactivity was decreased with the increased steric size of α-substituent R. Especially so toward the olefins which have a bulky β-substituent. Thus α-methylated imine **158** was deprotonated with triethylamine in the presence of lithium bromide. The ylide generated reacted smoothly with dimethyl fumarate, methyl acrylate, and methacrylate to give cycloadducts **160**, but cycloaddition with methyl crotonate was decelerated (Scheme 44). Deprotonation of isopropyl-substituted imine ester **161** can be achieved with DBU and lithium bromide. The ylide generated from **161** underwent diastereoselective cycloadditions only to the olefins bearing no β-substituent. Cycloadduct **162** is an example.



Scheme 44

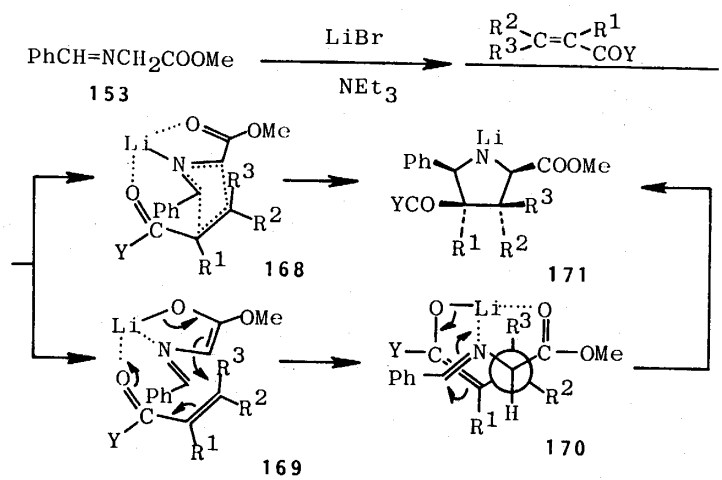
The imine amides derived from α-amino amides can be similarly activated with triethylamine plus lithium bromide, and the resulting ylides undergo selective cycloadditions with olefinic esters. For example, imine **163** reacts with methyl acrylate, methacrylate, and crotonate to provide **164** (Scheme 45). On the contrary, a secondary amide **165** afforded a mixture of stereoselective cycloadducts **166** and Michael adducts **167** in its reactions with methyl acrylate and crotonate.



Scheme 45

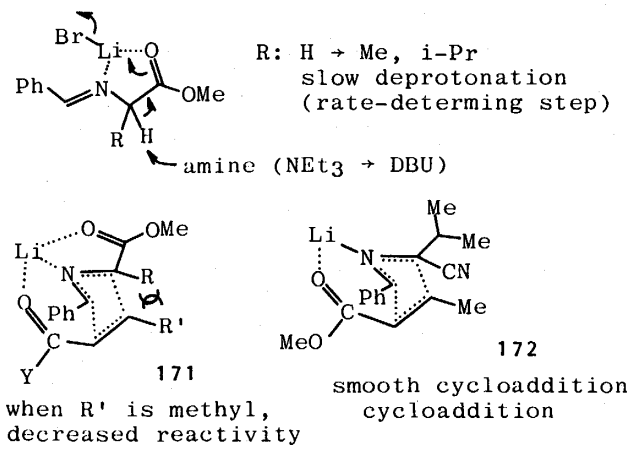
A possible reaction mechanism for the diastereoselective cycloadditions of *N*-lithiated azomethine ylides of the ester-stabilized types is presented with an example of imine **153** (Scheme 46). Coordination of the lithium metal to the carbonyl oxygen of olefins in the transition state, **168** and **169,** determines cis configuration between the phenyl and the carbonyl (COY) moieties in **171.** In these cases again the concerted (**168** → **171**) and the stepwise cycloaddition pathways (**169** → **170** → **171**) are possible, however their discrimination is not important since they are almost equivalent pathways from the standpoint of diastereoselectivity.

As briefly mentioned adove, easiness of α-deprotonation of imine esters depends upon steric size of the α-substituent R as well as basicity of the base employed. The substituent R causes steric repulsion against β-substituent R′ of olefins. When R is hydrogen, the α-deprotonation of imine **153** with triethylamine is a rate-determing step. Accordingly its cycloadditions take



Scheme 46

place at the same rate for different olefins. When R is methyl (in the case of imine **158**), the α-deprotonation is still rate-determing for β-unsubstituted olefinic esters. However, its cycloadditions to β-substituted olefins are extremely decelerated because of steric repulsion, the deprotonation step and the cycloaddition step being competitive. In the case of imine **161** bearing a bulky isopropyl moiety, DBU is needed for the α-deprotonation. Cycloaddition occurs only with the olefins carrying no β-substituent (Scheme 47).



Scheme 47

Such decreased reactivity of imine esters **158** and **161** toward methyl crotonate makes a striking contrast with the unchanged reactivity of cyano-stabilized ylides **128** (R=Ph, R^1=*i*-Pr) which was already described in Scheme 36. This difference presumably comes from different configuration of the *N*-lithiated ylide speices. As the ester-stabilized ylides take *E,E*-geometry, R and R′ are forced to be cis in the approach **171** bringing about serious steric repulsion. On the other hand, the cyano-stabilized ylides have *E,Z*-geometry. As shown with the approach **172**, sterically big isopropyl moiety does not cause steric repulsion against R′ (=Me), methyl and cyano moieties being cis in this case.

All of these works were accomplished in the laboratory of Professor Otohiko Tsuge who is about to finish his professorship at Kyushu University but to start a continued research and teaching in Kumamoto Institute of Technology. The present article is dedicated to him on the occasion of his retirement at age 63, with my greatest thanks for his useful advices and encouragement. Large contributions were made from the following collaborators: Dr K. Matsuda, Mr, A. Hatada, and Mr. T. Yamada always devoted themselves to the development of desilylative ylide generations. Mr. M. Ohe and Mr. K. Sakamoto succeeded to open a new entry to ester-stabilized and nonstabilized azomethine ylides by use of α-amino acids and derivatives. Dr. K. Ueno, Mr. K. Yorozu, and Mr. M. Moshioka were involved in the study of *N*-metalated azomethine ylides. The author is grateful to all of them for their zealous collaboration.

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