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Metallic Base-Induced Cycloadditions of *N*-(1-Cyanoalkyl)imines via *N*-Metalated Azomethine Ylides: Enhanced Reactivity and High Regio- and Stereoselectivity

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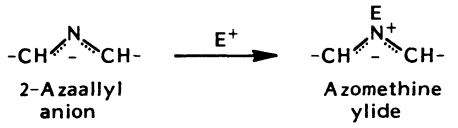
Lithiation of *N*-(1-cyanoalkyl)imines with LDA generates new *N*-lithiated azomethine ylide 1,3-dipoles which show enhanced reactivity toward dipolarophiles. They undergo exclusively regio- and stereoselective 3+2 cycloaddition reaction with α,β-unsaturated esters to give 1-pyrrolines after the elimination of LiCN. Metallic bases other than LDA can be also effective. Such high regio- and stereoselectivity is explained by the involvement of *N*-metalated azomethine ylides.

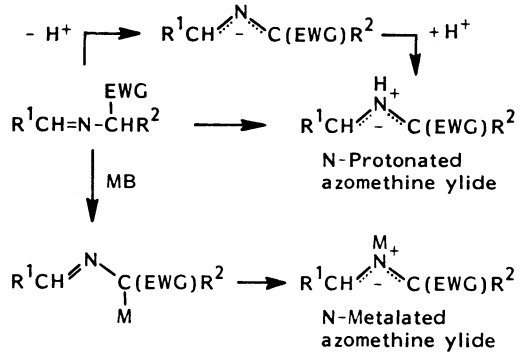
A 1,3-anionic cycloaddition of 2-azaallyl anions leading to five-membered nitrogen heterocycles was pioneered by Kauffmann.[1] Though this reaction with olefins looked promising as a method for the preparation of pyrrolidine skeletons, the difficulty of structural modification of 2-azaallyl anions[2] and the serious limitation of anionophiles employable[3,4] have discouraged its wide applications to heterocyclic synthesis. If an anion-stabilizing substituent is attached on the 1- and/or 3-carbon of 2-azaallyl anionic system, the anion generation by deprotonation of imines becomes easy.[5] However, such highly stabilized 2-azaallyl anions are known to undergo Michael addition rather than cycloaddition.[6,7]



(1)

Though complementary in a synthetic use, 2-azaallyl anions and azomethine ylides are isoelectronic, both carrying 4 pai conjugation along a carbon–nitrogen–carbon framework. The only difference is the presence of a pair of nonbonding electrons on the nitrogen of the anions. Accordingly, 2-azaallyl anions as hard nucleophiles can be converted into azomethine ylides as soft species if this electron pair is utilized to make a bond with an electrophile (E^+).

In the previous articles we have presented some examples in which both an azomethine ylide and a 2-azaallyl anion species can be generated from the common precursor.[8,9] Reactions of these anionic species with electron-deficient olefins frequently show reverse regioselectivity.



(2)

Imines of 2-amino esters[10] and 2-amino nitriles[9,11] are known to undergo a ready thermal tautomerization into rare *N*-protonated azomethine ylides. This tautomerization formally involves the deprotonation forming 2-azaallyl anions and the reprotonation at the imine nitrogen. Accordingly, metalation of imines with a metallic base (MB) would offer a new and general route to *N*-metalated azomethine ylides because the metal countercation (M^+) in the resulting 2-azaallyl anions is most likely to sit on the nitrogen rather than to stay on the carbon.[12]

The present article describes the first successful example for the generation of *N*-lithiated azomethine ylides by reaction of imines with LDA and their highly regio- and stereoselective cycloaddition with electron-deficient olefins. Use of metallic bases other than LDA is also discussed.

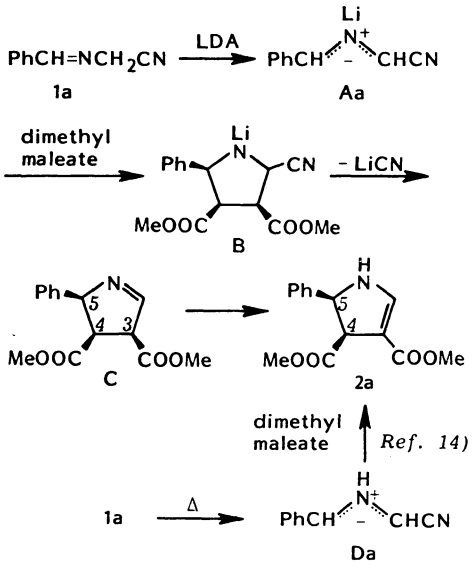
Results and Discussion

α-(Benzylideneamino)acetonitrile (**1a**) was treated with LDA (1 equiv) in dry THF at −78 °C turning bright red. This color faded away as immediately as dimethyl maleate was added. After 6 h at −78 °C the reaction was quenched with aqueous ammonium chloride to give dimethyl *cis*-5-phenyl-2-pyrroline-3,4-dicarboxylate (**2a**) in 71% yield as a single isomer (Scheme 1 and Table 1). As will be discussed later, this reaction involves the initial generation of *N*-lithiated azomethine ylide **Aa**, its stereoselective cycloaddition to dimethyl maleate forming cycloadduct **B**, and the quick elimination of LiCN leading to dimethyl *c*-5-phenyl-1-pyrroline-*r*-3,*c*-4-dicarboxylate (**C**). Ready double bond migration through an imine–enamine tautomerization[13] produced the isolated 2-pyrroline **2a**.

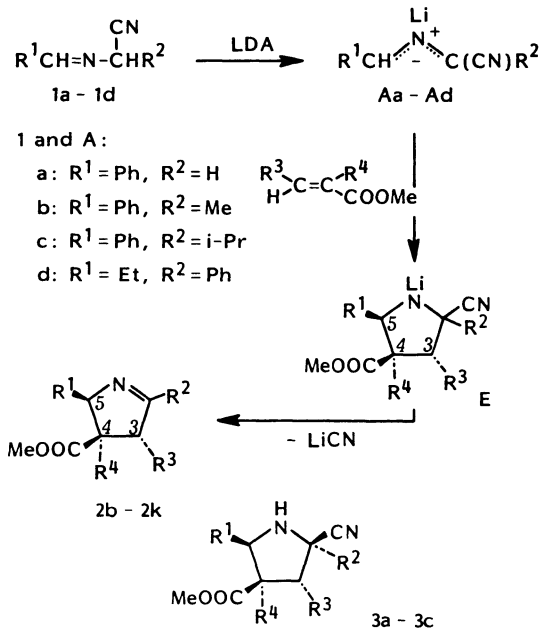
The same 2-pyrroline-3,4-dicarboxylate **2a** is also

available in 66% yield by a stereoselective cycloaddition of *N*-protonated azomethine ylide **Da** which can be generated more simply through a thermal tautomerization of **1a** (Scheme 1).[14] The advantage is that this LDA-induced cycloaddition can be performed at a low temperature (−78 °C), indicating the enhanced reactivity of *N*-lithiated azomethine ylide **Aa** compared to **Da**. We already know that only highly activated olefins such as maleimides, maleates, and fumarates are reactive with the *N*-protonated azomethine ylide **D**. The reaction with an acrylate does proceed, but only under harsh conditions and with a poor stereoselectivity.[14] Therefore it must be interesting to test the reactivity of *N*-lithiated azomethine ylide **Aa** toward such olefin esters as crotonates, cinnamates, and methacrylates which are known to be all inactive toward *N*-protonated ylide **Da**.

The ylide **Aa** was found to show an enhanced reactivity toward methyl acrylate, crotonate, cinnamate, and methacrylate (Scheme 2 and Table 1). The products isolated in high yields were either 1-pyrrolines **2b—2d** or pyrrolidines **3a** and **3b**. They are apparently the results from highly regio- and stereoselective cycloadditions of **Aa** with these olefins: 1-Pyrrolines **2b—2d** were produced by the elimination of LiCN and pyrrolidines **3a**, **3b** were derived by the protonation, both from the initial cycloadducts **E** in which 5-phenyl and 4-methoxycarbonyl are cis. High stereoselectivity with respect to the 2-position of **3a** as



Scheme 1.



Scheme 2.

Table 1. LDA-Induced Cycladdition of *N*-(1-Cyanoalkyl)imines **1a—1d**

N-(1-Cyanoalkyl)imine		Dipolarophile	Time/h[a]	Product(yield/%)[b]		R^1	R^2	R^3	R^4
PhCH=NCH$_2$CN	**1a**	MeOOCCH=CHCOOMe	6	**2a** (71)	**2a**	Ph	H	COOMe	H
		CH_2=CHCOOMe	4	**2b** (71)	**2b**	Ph	H	H	H
		MeCH=CHCOOMe	6	**2c** (43) + **3a** (45)	**2c**	Ph	H	Me	H
					3a	Ph	H	Me	H
		PhCH=CHCOOMe	6	**2d** (90)	**2d**	Ph	H	Ph	H
CN		CH_2=C(Me)COOMe	6	**3b** (100)	**3b**	Ph	H	H	Me
PhCH=NCHMe	**1b**	CH_2=CHCOOMe	8	**2e** (71)	**2e**	Ph	Me	H	H
		MeCH=CHCOOMe	7	**2f** (68)	**2f**	Ph	Me	Me	H
CN		CH_2=C(Me)COOMe	6	**2g** (100)	**2g**	Ph	Me	H	Me
PhCH=NCHPr-*i*	**1c**	MeCH=CHCOOMe	6	**2h** (20) + **3c** (52)[c]	**2h**	Ph	*i*-Pr	Me	H
CN					**3c**	Ph	*i*-Pr	Me	H
EtCH=NCHPh	**1d**	CH_2=CHCOOMe	6	**2i** (83)	**2i**	Et	Ph	H	H
		MeCH=CHCOOMe	6	**2j** (84)	**2j**	Et	Ph	Me	H
		CH_2=C(Me)COOMe	6	**2k** (83)	**2k**	Et	Ph	H	Me

a) At −78 °C in THF in the presence of LDA (1 equiv). b) Yield of isolated products. c) Cycloadduct **3c** eliminates HCN leading to **2h** when chromatographed over silica gel.

well as **3b** is surprising. This indicates the exclusive participation of one of two possible ylide isomers.[15]

Such high reactivity as well as excellent selectivity was maintained when alkylated imines, *N*-(1-cyanoethyl)imine **1b** and *N*-(1-cyano-2-methylpropyl)imine **1c**, were employed instead of **1a** (Scheme 2 and Table 1). The successful LDA-induced cycloaddition of **1c** indicates that even a bulky alkyl group may be introduced at the 2-position of 1-pyrrolines or pyrrolidines. Alkylated imines can be readily accessible from **1a** and alkyl halides in the presence of LDA.[9b]

Although α-(propylideneamino)phenylacetonitrile (**1d**) bears highly acidic α-hydrogens of imine (MeC<u>H</u>$_2$CH=N–), its lithiation with LDA took place smoothly at the carbon substituted by a cyano moiety to generate *N*-lithiated azomethine ylide **Ad**, indicating that the stability of *N*-lithiated azomethine ylide may be higher than that of *N*-lithio enamine. Similar cycloadditions of **Ad** with olefins produced **2i**—**2k** in excellent yields (Scheme 2 and Table 1).

The advantages of LDA-induced cycloaddition of *N*-(1-cyanoalkyl)imines **1** are summarized below (Scheme 3).

1) *N*-Lithiated azomethine ylide **Aa** is highly reactive to the olefin esters which can not react with *N*-protonated azomethine ylides **D**.

2) Alkylated ylides **Ab** and **Ac** are similarly reactive, while *N*-protonated counterparts **Db** and **Dc** are absolutely inactive even to maleimides as the most reactive dipolarophiles.

3) Smooth generation of ylide **Ad** is also possible.

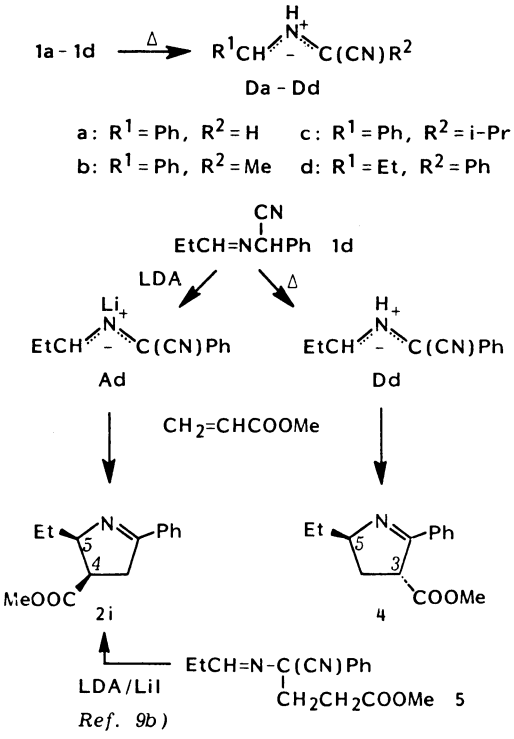
4) Cycloaddition of **A** takes place in a highly regio- and stereoselective manner.

5) In cycloadditions with methyl acrylate, both *N*-lithiated **Ad** and *N*-protonated azomethine ylides **Dd** show high regioselectivity, but their regiochemistry is opposite. Ylide **Ad** gave 4,5-disubstituted 1-pyrroline **2i** whose regiochemistry was assigned by an alternative synthesis from **5**,[9b] while 3,5-disubstituted 1-pyrroline **4** was obtained in the reaction of **Dd**.

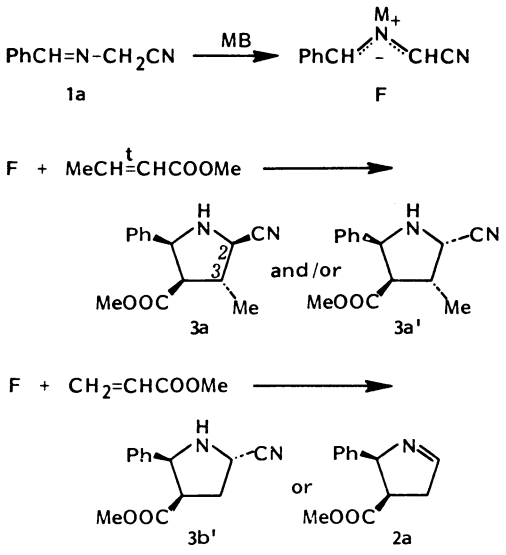
On the other hand, these LDA-induced cycloaddition route involves a disadvantage that the reaction has to be carried out under strongly basic conditions. The reactions of **Aa** with such olefins as maleimides, acrylonitrile, 3-buten-2-one, and phenyl vinyl sulfone led to the formation of polymeric products of olefins, warning that the olefinic dipolarophiles which are susceptible to bases may not be employed.

Metalation of *N*-(1-cyanoalkyl)imines **1** can be accomplished with other metallic bases. For example the reaction of **1a** with ethylmagnesium bromide generated *N*-magnesio azomethine ylide **F** (M=MgBr) which underwent cycloaddition with methyl acrylate or crotonate (Scheme 4 and Table 2). The products isolated as single isomers were pyrrolidines **3a′** and **3b′**, stereoisomers at the 2-position of **3**. The exclusive formation of **3′** indicates the selective participation of the anti form of ylide **F**. This makes a striking contrast with the exclusive participation of the syn form of *N*-lithio azomethine ylide **Aa** (see Scheme 2 and Table 1). Structures of **3a** and **3a′** were based upon the ^{13}C chemical shifts of 2-, 3-C, 2-CN, 3-Me as well as no NOE enhancement between 3-Me and 2-H of **3a′**.[16]

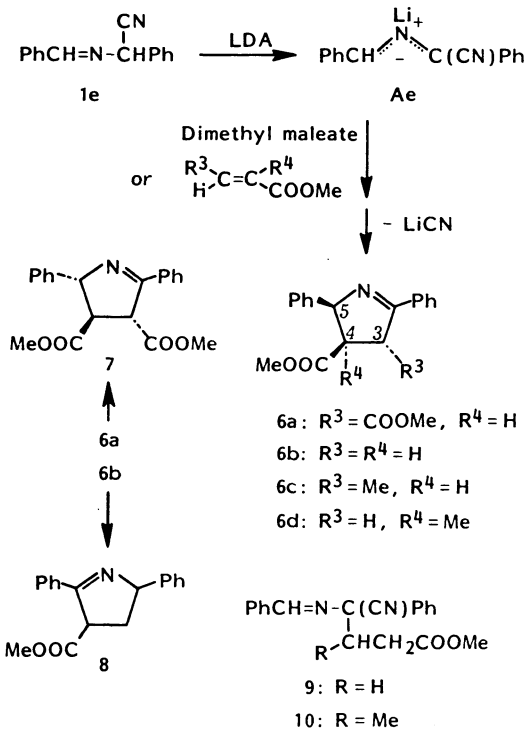
Treatment of ethylmagnesium bromide with an



Scheme 3.



Scheme 4.



Scheme 5.

equimolar amount of diisopropylamine forms magnesium bromide diisopropylamide.[17] This magnesium amide was also effective as a metallic base. *N*-Metalated azomethine ylide **F** (M=MgBr·HN(*i*-Pr)$_2$) was generated from **1a** and reacted with methyl acrylate to give 1-pyrroline **2a**. It is likely that the presence of diisopropylamine facilitated the elimination of MCN as observed in this case and also in the reactions of **A**. Accordingly generation of diisopropylamine-free *N*-lithiated azomethine ylides **F** (M=Li) was next examined.

Thus **1a** was first treated with butyllithium and then with methyl crotonate to produce a mixture of two stereoisomeric pyrrolidines **3a** and **3a'**. Further such other bases as *n*-BuLi/LiI, *n*-BuLi/NEt$_3$, and *n*-BuLi/Ti(OPr^i)$_4$ were employed. Isomer ratio **3a** : **3a'** depends upon the nature and amount of additives, and the highest selectivity for **3a'** was obtained (**3a**:**3a'**= 8 : 92) when triethylamine was used as an additive (Table 2).

N-Lithiated azomethine ylide **Ae** was generated from imine **1e** which bears two phenyl groups. Subsequent cycloadditions with dimethyl maleate, methyl acrylate, crotonate, and methacrylate produced 4,5-*cis*-1-pyrrolines **6a**—**6d** as the initial or isolated products (Scheme 5 and Table 3). The 5-H of 1-pyrrolines **6** is highly acidic because both the 2- and 5-positions are substituted by anion-stabilizing

Table 2. Reaction of α-(Benzylideneamino)acetonitrile (**1a**) with Metallic Bases Other than LDA

Base	Additive (equiv)	*N*-Metalated azomethine ylide **C**	Dipolarophile	Time/h[a]	Product (yield/%)[b]
EtMgBr	—	M=MgBr	MeCH=CHCOOMe	7	**3a'** (95)
	—	M=MgBr	CH_2=CHCOOMe	6	**3b'** (45)[c]
	HN(*i*-Pr)$_2$ (1)	M=MgBr·HN(*i*-Pr)$_2$	CH_2=CHCOOMe	6	**2a** (61)
n-BuLi	—	M=Li	MeCH=CHCOOMe	6	**3a** (45) + **3a'** (55)
	LiI (1)	M=Li·LiI	MeCH=CHCOOMe	6	**3a** + **3a'** (quant., 20:80)[d]
	LiI (1.5)	M=Li·LiI	MeCH=CHCOOMe	6	**3a** + **3a'** (quant., 11:89)[d]
	NEt$_3$ (1.1)	M=Li·NEt$_3$	MeCH=CHCOOMe	6	**3a** + **3a'** (quant., 8:92)[d]
	Ti(OPr^i)$_4$ (1)	e)	MeCH=CHCOOMe	6	**3a** + **3a'** (quant., 60:40)[d]

a) All reactions were carried out in dry THF at − 78 °C with each one equivalent amount of **1a**, an olefin, and a base. b) Yield of isolated products. c) Fifty five percent of **1a** was recovered. d) Isomer ratio was determined by ^{1}H NMR spectrum. e) The reacting species is not certain.

Table 3. LDA-Induced Cycloaddition of **1e**

Dipolarophile	Condition[a]	Product (yield/%)[b]
MeOOCCH=CHCOOMe	− 78 °C, 0.5 h	**6a** + **7** (80, 1 : 6)[c]
	− 78 °C, 4 h	**7** (89)
CH_2=CHCOOMe	− 78 °C, 4 h	**6b** (41) + **8** (13) + **9** (36)
	− 78 °C, 0.5 h then rt, 1 h	**6b** (59) + **8** (39)
MeCH=CHCOOMe	− 78 °C, 3 h	**6c** (46) + **10** (23)
CH_2=C(Me)COOMe	− 78 °C, 3 h	**6d** (61)

a) All reactions were performed in THF by using LDA (1 equiv). b) Yield of isolated products. c) Inseparable mixture. The product ratio was determined by ^{1}H NMR spectrum.

phenyl groups. Therefore **6a** experienced a ready epimerization at the 5-position into 4,5-*trans*-1-pyrroline **7** in the presence of LDA, presumably via a 2-azaallyl anion intermediate. Formation of **8**, a regioisomer of **6b**, as a side product in the reaction between **Ae** and methyl acrylate may have arisen from a similar 2-azaallyl anion intermediate. Some cycloadditions were accompanied by Michael adducts, for instance **9** and **10**.

It is clear that *N*-lithiated anionic species are involved in these LDA-induced cycloaddition reactions. These species should be refered to as *N*-lithiated azomethine ylides **A** because the nonbonding electron pair on the imine nitrogen has been utilized to make a nitrogen–lithium bond. The involvement of *N*-lithiated azomethine ylide **A** is confirmed on the ground of the following facts: a) High regio- and stereoselectivity can be well-interpreted by a chelation between the lithium metal on the imine nitrogen and the carbonyl oxygen; b) DBU-Induced Michael addition of **1a** with methyl acrylate gives not only the 1:1 adduct but also 1:2 adduct;[9b] c) DBU-Induced Michael addition of imine **1b** with methyl crotonate is poor in stereoselectivity, and of imine **1b** is sterically too hindered;[18] d) Michael adduct of **1b** to methyl crotonae does not cyclize leading to **2f** on treatment with LDA at −78 °C.[19]

Thus it is concluded that the LDA-induced cycloadditions of *N*-(1-cyanoalkyl)imines **1** proceed through a chelated transition state (Fig. 1). There are two possible paths, but we can not so far discriminate the following two routes: Path a: A concerted endo cycloaddition promoted by an attractive interaction between the ester carbonyl of the crotonate and the lithium metal of **A** (**G**→**J**); Path b: A sequence of Michael addition and intramolecular imine addition where the lithium metal migrates from the imine nitrogen to the ester oxygen so that high stereoselectivity may result (**H**→**I**→**J**). These two paths are virtually identical since the synchronousness of bond formations is only slightly different. The discrimination seems to be trivial.

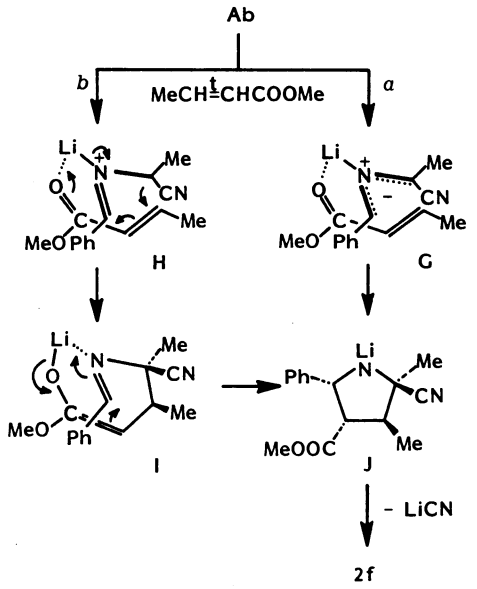


Fig. 1. Two possible mechanisms for the LDA-induced cycloaddition of **1b** to methyl crotonate.

Experimental

General. Melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were taken with a JASCO IRA-1 or a JASCO A-702 spectrometer. ^{1}H NMR spectra were recorded on a Hitachi R-40 (90 Hz) or a JEOL FX-100 instrument (100 MHz) and ^{13}C NMR on a JEOL FX-100 spectrometer at 25.05 MHz. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. Mass spectra were measured with a JEOL-01SG-2 spectrometer at 70 eV of ionization energy. High resolution mass spectra were obtained on the same instrument. Elemental analyses were performed on a Hitachi 026 CHN analyzer. Thin-layer chromatography (TLC) was accomplished on 0.2 mm precoated plates of silica gel 60 F-254 (Merck). Visualization was made with ultraviolet light (254 and 365 nm), iodine, molybdophosphoric acid (5% in ethanol), or *p*-anisaldehyde (5% in ethanol containing 5% of sulfuric acid). For preparative column chromatography, Wakogel C-200, C-300 (Wako), and Silicagel 60 (Merck) were employed. Solvents were evaporated with a Tokyo Rikakikai rotary evaporator type-V at about 50 °C unless otherwise stated.

Imine **1a** or **1d** was prepared from the reaction of aminoacetonitrile or α-aminophenylacetonitrile with the corresponding aldehyde;[9a] **1b** and **1c** were available by alkylation of **1a**.[9b] Tetrahydrofuran (THF) was dried over sodium and distilled on sodium wire immediately before use.

General Procedure for LDA-Induced Cycloaddition of *N*-(1-Cyanoalkyl)imines 1a—1d with Electron-Deficient Olefins Leading to 2b—2k and/or 3a—3c. The reaction of α-(benzylideneamino)acetonitrile **1a** with dimethyl maleate is described as a typical example: To a solution of lithium diisopropylamide (LDA, 2.2 mmol) freshly prepared from butyllithium and diisopropylamine in dry THF (10 ml) was added slowly imine **1a** (0.29 g, 2.01 mmol in THF (2 ml)) at −78 °C. After 5 min at the same temperature, dimethyl maleate (0.316 g, 2.19 mmol in THF (0.5 ml)) was added. The mixture was allowed to stir at −78 °C under nitrogen for 6 h, poured into saturated ammonium chloride, and extracted with diethyl ether (30 ml×3). The combined extracts were dried over anhydrous mgnesium sulfate and evaporated in vacuo. The residue (0.433 g) was chromatographed over silica gel by using chloroform–diethyl ether (5 : 1) to give 2-pyrroline **2a** (0.372 g, 71%).

Other LDA-induced cycloadditions of **1a—1d** with olefins were carried out under the reaction conditions listed in Table 1 in which the results are also summarized.

2a: Colorless prisms (benzene–hexane); mp 120—122 °C; IR (KBr) 3300, 1720, and 1670 cm^{-1}; ^{1}H NMR ($CDCl_3$)

δ=3.08 (3H, s, 4-COOMe), 3.61 (3H, s, 3-COOMe), 4.12 (1H, dd, J=12.3 and 1.0 Hz, 4-H), 4.84 (1H, br, NH), 5.30 (1H, dd, J=12.3 and 1.6 Hz, 5-H), 7.2—7.4 (5H, m, Ph), and 7.46 (1H, dd, J=3.0 and 1.0 Hz, 2-H); ^{13}C NMR ($CDCl_3$) δ=50.48, 51.12 (each q, COOMe), 52.14 (d, 4-C), 66.08 (d, 5-C), 100.29 (s, 3-C), 127.14, 127.96 (each d), 137.66 (s), 150.62 (d, 2-C), 166.07, and 171.24 (each s, COOMe); MS *m/z* (rel intensity, %) 261 (M^+, 35), 202 (base peak), 170 (45), 143 (50), 117 (21), and 115 (34). Found: C, 64.38; H, 5.84; N, 5.57%. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36%.

2b: Pale yellow liquid; IR (neat) 1730 and 1625 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.80 (2H, m, 3-H), 3.08 (3H, s, COOMe), 3.50 (1H, ddd, J=9.6, 9.2, and 6.0 Hz, 4-H), 5.52 (1H, ddd, J=9.2, 4.0, and 2.0 Hz, 5-H), 7.0—7.4 (5H, m, Ph), and 7.80 (1H, dt, J=2.0, 1.0, and 1.0 Hz, 2-H); ^{13}C NMR ($CDCl_3$) δ=40.24 (t, 3-C), 46.30 (d, 4-C), 51.36 (q, COOMe), 78.83 (d, 5-C), 127.66, 128.13 (each d), 138.07 (s), 167.24 (d, 2-C), and 172.65 (s, COOMe); MS *m/z* (rel intensity, %) 203 (M^+, 15), 144 (34), 143 (20), 117 (42), 90 (23), and 43 (base peak). HRMS Found: *m/z* 203.0932. Calcd for $C_{12}H_{13}NO_2$: M, 203.0945.

2c: Pale yellow liquid; IR (neat) 1740 and 1625 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.22 (3H, d, J=7.1 Hz, Me), 3.06 (1H, dd, J=9.5 and 7.0 Hz, 4-H), 3.15 (3H, s, COOMe), 3.4—3.7 (1H, m, 3-H), 5.60 (1H, dt, J=9.5, 2.0, and 2.0 Hz, 5-H), 7.0—7.4 (5H, m, Ph), and 7.66 (1H, br s, 2-H); ^{13}C NMR ($CDCl_3$) δ=16.06 (q, Me), 46.77 (d, 3-C), 51.24 (q, COOMe), 55.24 (d, 4-C), 78.42 (d, 5-C), 127.54, 127.71, 128.13 (each d), 137.60 (s), and 172.01 (d and s, 2-C and COOMe); MS *m/z* (rel intensity, %) 217 (M^+, 11), 158 (44), 157 (21), 130 (20), 129 (23), 128 (25), 117 (91), 116 (40), 115 (46), 104 (29), 103 (23), 91 (54), 90 (base peak), 89 (78), 77 (51), 69 (78), 63 (44), 59 (58), 54 (26), 52 (48), 42 (55), and 40 (56). HRMS Found: *m/z* 217.1097. Calcd for $C_{13}H_{15}NO_2$: M, 217.1100.

2d: Pale yellow liquid; IR (neat) 1740 and 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=3.14 (3H, s, COOMe), 3.44 (1H, dd, J=9.5 and 7.8 Hz, 4-H), 4.67 (1H, ddd, J=7.8, 3.0, and 2.0 Hz, 3-H), 5.75 (1H, dt, J=9.5, 2.0, and 2.0 Hz, 5-H), 6.9—7.6 (10H, m, Ph), and 7.76 (1H, dd, J=3.0 and 2.0 Hz, 2-H); ^{13}C NMR ($CDCl_3$) δ=51.36 (q, COOMe), 56.83 (d, 4-C), 57.71 (d, 3-C), 78.83 (d, 5-C), 127.54, 127.66, 127.77, 128.18, 128.83, 129.19 (each d), 136.95, 138.77 (each s), 169.19 (d, 2-C), and 171.48 (s, COOMe); MS *m/z* (rel intensity, %) 279 (M^+, 13), 220 (23), 163 (25), 158 (22), 131 (29), 117 (83), 115 (30), 105 (53), 90 (31), 85 (67), 83 (base peak), 77 (41), and 47 (25). Stability of this compound was not enough for the molecular weight measurement by HRMS.

2e: Pale yellow liquid; IR (neat) 1730 and 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.19 (3H, d, J=2.0 Hz, Me), 2.68 (1H, dd, J=17.5 and 9.5 Hz, one of 3-H), 3.0—3.3 (1H, m, the other of 3-H), 3.08 (3H, s, COOMe), 3.56 (1H, dt, J=9.5 and 6.0 Hz, 4-H), 5.44 (1H, dd, J=9.5 and 2.0 Hz, 5-H), and 7.0—7.4 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=19.47 (q, Me), 41.94 (t, 3-C), 48.36 (d, 4-C), 51.24 (q, COOMe), 78.30 (d, 5-C), 127.54, 128.07 (each d), 138.77 (s), 172.76 (s, COOMe), and 175.83 (s, 2-C); MS *m/z* (rel intensity, %) 217 (M^+, 11), 158 (38), 157 (29), 131 (61), 130 (67), 116 (29), 115 (61), 104 (36), 103 (24), 91 (31), 90 (base peak), 89 (85), 77 (40), 63 (40), 59 (20), 55 (81), 51 (44), and 38 (46). HRMS Found: *m/z* 217.1068. Calcd for $C_{13}H_{15}NO_2$: M, 217.1084.

2f: Pale yellow liquid; IR (neat) 1735 and 1645 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.18 (3H, d, J=7.0 Hz, 3-Me), 2.30 (3H, s, 2-Me), 3.13 (3H, s, COOMe), 3.1—3.5 (1H, m, 4-H), 3.6—3.7 (1H, m, 3-H), 5.36 (1H, d, J=9.5 Hz, 5-H), and 7.0—7.4 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=16.53, 17.59 (each q, Me), 30.94 (d, 4-C), 47.89 (d, 3-C), 51.36 (q, COOMe), 57.00 (d, 5-C), 127.54, 127.71, 128.18 (each d), 138.48 (s), 172.42 (s, COOMe), and 179.42 (s, 2-C); MS *m/z* (rel intensity, %) 231 (M^+, 45), 172 (13), 131 (base peak), 130 (39), and 90 (26). HRMS Found: *m/z* 231.1255. Calcd for $C_{14}H_{17}NO_2$: M, 231.1257.

2g: Pale yellow liquid; IR (neat) 1730 and 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.48 (3H, s, 4-Me), 2.17 (3H, d, J=1.8 Hz, 2-Me), 2.19 (1H, d, J=17.8 Hz, one of 3-H), 3.04 (3H, s, COOMe), 3.42 (1H, dd, J=17.8 and 1.1 Hz, the other of 3-H), 4.95 (1H, br s, 5-H), and 7.0—7.4 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=19.30 (q, 3-Me), 24.65 (q, 2-Me), 49.65 (t, 3-C), 50.89 (q, COOMe), 54.65 (s, 4-C), 85.89 (d, 5-C), 126.89, 127.19, 127.54 (each d), 138.54 (s), 174.01, and 174.89 (each s, 2-C and COOMe); MS *m/z* (rel intensity, %) 231 (M^+, 12), 131 (base peak), 130 (46), 90 (50), 89 (33), and 41 (22). HRMS Found: *m/z* 231.1265. Calcd for $C_{14}H_{17}NO_2$: M, 231.1270.

2h: Yellow liquid; IR (neat) 1740 and 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.2—1.3 (9H, m, Me and *i*-Pr), 2.6—2.9 (1H, m, *i*-Pr), 3.12 (1H, dd, J=9.5 and 7.2 Hz, 4-H), 3.16 (3H, s, COOMe), 3.3—3.7 (1H, d, J=9.5 Hz, 5-H), and 7.0—7.5 (5H, m, Ph); MS *m/z* (rel intensity, %) 259 (M^+, 58), 159 (base peak), 131 (28) 117 (70), 91 (21), and 90 (21). HRMS Found: *m/z* 259.1609. Calcd for $C_{16}H_{21}NO_2$: M, 259.1645.

2i: Pale yellow liquid; IR (neat) 1735 and 1625 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.12 (3H, q, J=7.0 Hz, Et), 1.4—1.8 (2H, m, Et), 3.0—3.6 (3H, m, 3- and 4-H), 3.68 (3H, s, COOMe), 4.3—4.4 (1H, m, 5-H), 7.3—7.5 (3H, m, Ph), and 7.7—7.9 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=11.65 (q, Et), 25.41 (t, Et), 38.12 (t, 3-C), 45.83 (d, 4-C), 51.65 (q, COOMe), 75.95 (d, 5-C), 127.95, 128.65, 130.83 (each d), 134.30 (s), 171.13, and 173.77 (each s, 2-C and COOMe); MS *m/z* (rel intensity, %) 231 (M^+, 4), 172 (24), 144 (27), 143 (47), 130 (base peak), 117 (24), 116 (33), 115 (92), 104 (97), 77 (62), and 51 (37). HRMS Found: *m/z* 231.1250. Calcd for $C_{14}H_{17}NO_2$: M, 231.1244.

2j: Pale yellow liquid; IR (neat) 1735 and 1620 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ=1.14 (3H, q, J=7.0 Hz, Et), 1.22 (3H, d, J=7.0 Hz, Me), 1.4—1.8 (2H, m, Et), 3.00 (1H, dd, J=8.0 and 4.2 Hz, 4-H), 3.6—4.0 (1H, m, 3-H), 3.64 (3H, s, COOMe), 4.32 (1H, q, J=8.0 Hz, 5-H), 7.2—7.5 (3H, m, Ph), and 7.6—7.9 (2H, m, Ph); ^{13}C NMR($CDCl_3$) δ=11.82 (q, Et), 17.41 (q, Me), 25.35 (t, Et), 45.83 (d, 4-C), 51.47 (q, COOMe), 54.77 (d, 3-C), 74.01 (d, 5-C), 128.18, 128.60, 130.42 (each d), 133.60 (s), 173.72, and 175.66 (each s, 2-C and COOMe); MS *m/z* (rel intensity, %) 245 (M^+, 8), 156 (31), 145 (23), 130 (79), 115 (30), 104 (base peak), 103 (30), 91 (36), 77 (64), 51 (46), and 41 (55). HRMS Found: *m/z* 245.1413. Calcd for $C_{15}H_{19}NO_2$: M, 245.1143.

2k: Pale yellow liquid; IR (neat) 1730 and 1625 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ=1.10 (3H, q, J=7.5 Hz, Et), 1.38 (3H, s, Me), 1.3—1.8 (2H, m, Et), 2.76 (1H, d, J=17.0 Hz, one of 3-H), 3.64 (1H, dd, J=17.0 and 2.0 Hz, the other of 3-H), 3.66 (3H, s COOMe), 3.8—4.1 (1H, m, 5-H), 7.3—7.5 (3H, m, Ph), and 7.7—7.9 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=11.77 (q, Et), 25.12 (t, Et), 25.59 (q, Me), 46.00 (t, 3-C), 52.00 (q, COOMe), 83.77 (d, 5-C), 127.83, 128.60, 130.72 (each d), 134.54 (s), 170.84 (s, COOMe), and 175.66 (s, 2-C); MS *m/z* (rel intensity, %) 245 (M^+, 9), 186 (20), 157 (23), 156 (32), 130 (base peak), 104 (95), 77 (60), and 41 (49). HRMS Found: *m/z*

245.1422. Calcd for $C_{15}H_{19}NO_2$: M, 245.1428.

3a: Pale yellow liquid; IR (neat) 3360, 2230, and 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.22 (3H, d, J=7.0 Hz, Me), 2.0—2.4 (1H, br, NH), 2.94 (1H, ddd, J=9.0, 7.0, and 5.5 Hz, 3-H), 3.10 (1H, dd, J=8.7 and 5.5 Hz, 4-H), 3.21 (3H, s, COOMe), 3.66 (1H, d, J=9.0 Hz, 2-H), 4.63 (1H, d, J=8.7 Hz, 5-H), and 7.1—7.4 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=15.94 (q, Me), 40.89 (d, 3-C), 51.47 (q, COOMe), 54.24 (d, 4-C), 56.59 (d, 2-C), 63.24 (d, 5-C), 120.24 (s, CN), 127.36, 127.89, 128.18 (each d), 140.18 (s), and 171.13 (s, COOMe); MS m/z (rel intensity, %) 244 (M^+, 5), 144 (56), 143 (76), 117 (32), 116 (36), 115 (32), 104 (29), 91 (45), 90 (26), 89 (35), 78 (24), 77 (50), 69 (base peak), 59 (53), 58 (24), 56 (20), 52 (33), 44 (25), 42 (77), and 40 (49). HRMS Found: m/z 244.1212. Calcd for $C_{14}H_{16}N_2O_2$: M, 244.1212.

3b: Colorless liquid; IR (neat) 3350, 2240, and 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.45 (3H, s, Me), 2.02 (1H, dd, J=13.4 and 4.5 Hz, one of 3-H), 2.54 (1H, br s, NH), 3.04 (1H, dd, J=13.4 and 8.5 Hz, the other of 3-H), 3.17 (3H, s, COOMe), 4.22 (1H, s, 5-H), 4.45 (1H, dd, J=8.5 and 4.5 Hz, 2-H), and 7.0—7.4 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=21.94 (q, Me), 41.41 (t, 3-C), 45.94 (d, 2-C), 51.06 (q, COOMe), 53.83 (s, 4-C), 72.12 (d, 5-C), 121.66 (s, CN), 126.54, 127.83 (each d), 137.48 (s), and 173.90 (s, COOMe); MS m/z (rel intensity, %) 244 (M^+, 7), 144 (base peak), 143(86), 117 (26), and 116 (24). HRMS Found: m/z 244.1200. Calcd for $C_{14}H_{16}N_2O_2$: M, 244.1190.

3c: Formation of this compound **3c** was only observed in the ^1H NMR spectrum of crude reaction mixture obtained from **1c** and methyl crotonate. When chromatographed over silica gel by using chloroform–diethyl ether (10 : 1 vol/vol), ready elimination of HCN took place and 72% yield of **2h** was isolated. The ratio between **2h** and **3c** was determined by the ^1H NMR of the crude mixture. ^1HNMR ($CDCl_3$) δ=3.03 (s, COOMe) and 4.65 (dd, J=10.0 and 5.5 Hz, 5-H).

Cycloaddition of 1a Induced by Metallic Bases Other than LDA. Preparation procedure for the *N*-metalated species from **1a** is as follows. All the procedures were conducted under dry nitrogen at −78 °C:

EtMgBr: To EtMgBr (2.2 mmol) freshly prepared in THF (7 ml) was added **1a** (0.295 g, 2.05 mmol in THF (2 ml)). An olefin (2.2 mmol) was added after 15 min.

EtMgBr/HN(*i*-Pr)$_2$: To EtMgBr (2.2 mmol in THF (8 ml)) was added diisopropylamine (2.2 mmol in THF (10 ml)) and then **1a** (0.29 g, 2.01 mmol in THF (2 ml)). After 14 min, methyl acrylate (0.19 g, 2.21 mmol) was added.

***n*-BuLi**: To *n*-BuLi (1 M† solution in hexane, 2.2 ml, 2.2 mmol) in THF (5 ml) was added **1a** (0.151 g, 1.05 mmol). After 5 min, methyl crotonate (0.123 g, 1.23 mmol in THF (1 ml)) was added.

***n*-BuLi/LiI, *n*-BuLi/NEt$_3$, or *n*-BuLi/Ti(OPr^i)$_4$**: To LiI (1 mmol or 1.5 mmol), NEt_3 (1.11 mmol), or $Ti(OPr^i)_4$ (1 mmol) in THF (5 ml) was added *n*-BuLi (1.1 mmol). Imine **1a** (0.147 g, 1.02 mmol) was added after 10 min and then the mixture was stirred for an additional 10 min before methyl crotonate (0.115 g, 1.15 mmol) was introduced.

Subsequent cycloadditions were conducted under the conditions listed in Table 2 and the results are shown in the same table. The data for **2a** and **3a** were already presented above.

3a′: Colorless prisms (benzene–hexane); mp 96—97 °C; IR (KBr) 3350, 2230, and 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.26 (3H, d, J=6.5 Hz, Me), 2.40 (br s, NH), 2.9—3.2 (2H, m, 3-and 4-H), 3.10 (3H, s, COOMe), 4.36 (1H, d, J=6.0 Hz, 2-H), 4.81 (1H, d, J=9.1 Hz, 5-H), and 7.1—7.3 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=15.18 (q, Me), 38.30 (d, 3-C), 51.47 (q, COOMe), 54.18 (d, 4-C), 55.24 (d, 2-C), 62.77 (d, 5-C), 119.30 (s, CN), 127.71, 128.18 (each d), 139.83 (s), and 171.78 (s, COOMe); MS m/z (rel intensity, %) 244 (M^+, 16), 163 (39), 145 (base peak), and 144 (77). Found: C, 68.99; H, 6.72; N, 11.42%. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47%.

3b′: Colorless needles (diethyl ether–hexane); mp 78.5—79 °C; IR (KBr) 3330, 2230, and 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.00 (1H, br s, NH), 2.32 (1H, ddd, J=13.0, 8.5, and 3.0 Hz, one of 3-H), 2.72 (1H, ddd, J=13.0, 8.0, and 7.0 Hz, the other of 3-H), 3.13 (3H, s, COOMe), 3.41 (1H, dt, J=8.5, 8.5, and 7.0 Hz, 4-H), 4.44 (1H, dd, J=8.0 and 3.0 Hz, 2-H), 4.72 (1H, d, J=8.5 Hz, 5-H), and 7.23 (5H, s, Ph); MS m/z (rel intensity, %) 230 (M^+, 2), 144 (88), 143 (base peak), 142 (23), 117 (61), 116 (51), 115 (63), 104 (49), 91 (33), 90 (45), 89 (66), 78 (22), 77 (68), 66 (24), 65 (25), 63 (27), 55 (67), 51 (51), 50 (20), and 38 (44). Found: C, 67.72; H, 6.13; N, 12.05%. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17%.

General Procedure for LDA-Induced Cycloddition of 1e Leading to 6—10. To a solution of LDA freshly prepared from butyllithium (1.5 mmol) and diisopropylamine in THF (3 ml) was added imine **1e** (0.33 g, 1.5 mmol) at −78 °C in a period of 2 min. After 5 min, an olefin (1.6 mmol) was added to this red solution and the mixture was stirred under the conditions shown in Table 3. The reaction mixture was poured into ice water and extracted with diethyl ether (25 ml×2). The combined extracts were dried over magnesium sulfate and evaporated in vacuo. The residue was chromatographed over silica gel. All the results are listed in Table 3. Products **6a**, **6b**, **7**, and **8** have been already prepared from the reactions of *N*-protonated azomethine ylide derived from **1e**,[9a] and Michael adducts **9** and **10** are also known.[9b]

6c: Colorless prisms (hexane); mp 152—153 °C; IR (KBr) 1730 and 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.26 (3H, d, J=7.0 Hz, Me), 3.06 (3H, s, COOMe), 3.25 (1H, dd, J=9.0 and 4.0 Hz, 4-H), 4.00 (1H, ddd, J=7.0, 4.0, and 2.0 Hz, 3-H), 5.56 (1H, dd, J=9.0 and 2.0 Hz, 5-H), 7.0—7.4 (8H, m, Ph), and 7.7—7.9 (2H, m, Ph); MS m/z (rel intensity, %) 293 (M^+, 28), 234 (41), 193 (base peak), 115 (26), 91 (43), and 77 (27). Found: C, 77.78; H, 6.54; N, 5.01%. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77%.

6d: Colorless liquid; IR (neat) 1730 and 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.60 (3H, s, Me), 2.80 (1H, d, J=18.0 Hz, one of 3-H), 3.13 (3H, s, COOMe), 3.90 (1H, dd, J=18.0 and 2.0 Hz, the other of 3-H), 5.23 (1H, d, J=2.0 Hz, 5-H), 7.0—7.5 (8H, m, Ph), and 7.95 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=25.59 (q, Me), 46.18 (t, 3-C), 51.47 (q, COOMe), 54.71 (s, 4-C), 86.59 (d, 5-C), 127.54, 127.83, 128.13, 128.77, 131.24 (each d), 134.07, 138.72 (each s), 173.72, and 174.54 (each s, 2-C and COOMe); MS m/z (rel intensity, %) 293 (M^+, 21), 234 (26), 193 (base peak), 165 (21), 103 (29), 90 (49), and 89 (57). HRMS Found: m/z 293.1415. Calcd for $C_{19}H_{19}NO_2$: M, 293.1425.

† 1M=1 mol dm^{-3}.

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14) Refs. 9a and 11b.

15) Each one isomer of the anti and syn forms of *N*-lithiated azomethine ylides **Aa** may join in cycloadditions (see Ref. 9a). The exclusive participation of the anti isomer of **Aa** took place in these cases.

16) Similar structural assignment based upon ^{13}C chemical shifts and NOE enhancement has been discussed in the preceding article (Ref. 9b).

17) T. Hiyama and K. Kobayashi, *Tetrahedron Lett.*, **23**, 1567 (1982).

18) DBU-Induced Michael addition of **1c** to methyl crotonate never takes place even when the reaction mixture was heated under reflux in THF for 10 h. The Michael adduct of **1b** is a mixture of two diastereomers (Ref. 9b).

19) Only one stereoisomer of the Michael adduct of **1b** to methyl crotonate smoothly cyclizes into **2f** only in the presence of lithium iodide at −78 °C. The other isomer is recovered intact (Ref. 9b).