Generation of an *N*-Sodioazomethine Ylide and Its Cycloadditions with α,β-Unsaturated Esters

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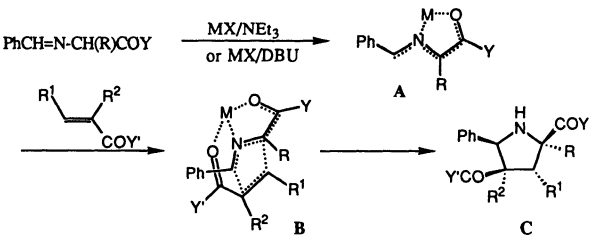
Treatment of methyl 2-(benzylideneamino)propanoate with sodium hydride in THF generates an *N*-sodioazomethine ylide, which shows a very poor stereoselectivity in the cycloaddition with methyl acrylate. However, addition of such a base as triethylamine or *t*-butyl alcohol improves the selectivity. Chemical properties of the ylide have been discussed on the basis of the selectivity totally different from that of *N*-lithio analogue.

N-Metalated azomethine ylides **A**, the ylide of new type, can be generated upon treatment of imines [PhCH=NCH(R)COY] of α-amino esters and amides with tertiary amines in the presence of metal halides.[1-3] These ylides show increased reactivity in their cycloadditions and high reliability in stereochemical selectivities. A variety of metals such as lithium, magnesium, zinc, aluminum, and silver can be incorporated; metal-chelated intermediates **B** are responsible for the highly stereoselective cycloadditions with carbonyl-activated olefins [$R^1CH=C(R^2)COY'$] leading to **C**.



In this ylide generation scheme, ylide species **A** are always accompanied by the formation of an equimolar amount of acidic products, trialkylammonium halides, which can act as a quencher of the anionic intermediates involved. Therefore, the ylide generation using tertiary amine is a reversible process, causing the undesired formation of Michael adducts.[2]

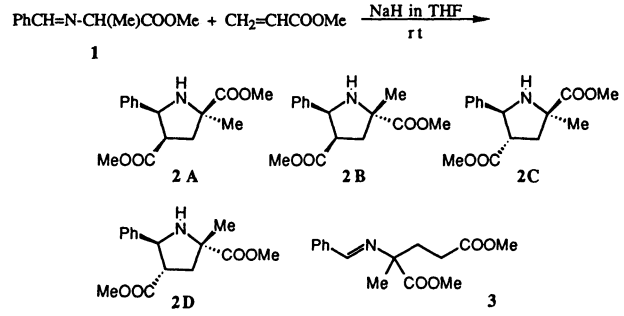
Irreversible ylide generation would be achieved if imines of α-amino esters are treated with metallic bases such as lithium diisopropylamide, butyllithium, and sodium hydride.[4] The ylides generated in high concentration are expected to show a much more enhanced reactivity.

In the present article, reactions of an imine of α-amino ester, methyl 2-(benzylideneamino)propanoate (**1**), with a variety of olefins in the presence of sodium hydride have been examined. Although cycloaddition of the resulting *N*-sodioazomethine ylide with methyl acrylate shows a poor stereoselectivity, addition of triethylamine or *t*-butyl alcohol as a base improves the selectivity. A stepwise cyclization mechanism is proposed since metal chelation is less important. Stereoselectivities are mainly determined at the step of intramolecular nucleophilic imine addition.

Results and Discussion

It was previously reported that treatment of imine **1** with triethylamine and sodium iodide generated the *N*-sodioazomethine ylide.[2] Its reaction with methyl acrylate produced a 1:2.7 mixture of stereoselective cycloadduct **2A** and Michael adduct **3** in a combined yield of 96%, indicating highly ionic character of the transition state rather than a tightly chelated structure.

On the other hand, reaction of imine **1** with methyl acrylate in the presence of sodium hydride, in tetrahydrofuran (THF) at room temperature, gave three isomeric 1:1 cycloadducts **2A—C** in 45, 13, and 6% yields, respectively, along with the Michael adduct **3** (25%, Scheme 1 and Entry 1 in Table 1). These three isomers **2A—C** could be separated from each other through column chromatography over silica gel.



Scheme 1.

Figure 1 shows ^1H NMR spectral data of **2A—C** and the last possible isomeric cycloadduct **2D** whose formation is to be described later. Isomer **2A** is identical with 2,4-*cis*:4,5-*cis*-2,4-pyrrolidinedicarboxylate which was previously obtained as a single isomer in the reaction of **1** with methyl acrylate in the presence of lithium bromide and triethylamine.[1] Isomer **2B** was determined to be a 2,4-trans:4,5-cis structure on the basis of the following spectral data

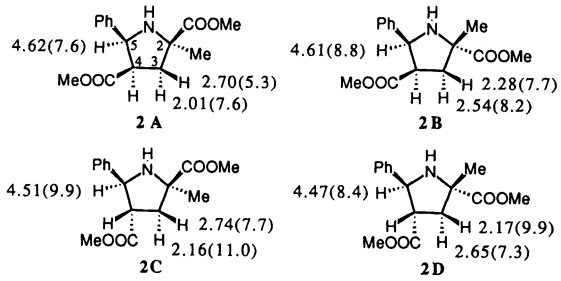


Fig. 1. Structural assignment of isomeric cycloadducts **2A—D** on the basis of ^{1}H NMR spectral data with vicinal coupling constants in Hz in parentheses.

(Fig. 1), and hence the reported 2,4-cis:4,5-cis geometry of **2A** was reconfirmed: 1) The ester methyl at the 4-position (4-COOMe, δ=3.12) is shielded by 5-Ph, 2) the difference of chemical shifts of 3-Hs (2.54—2.28=0.26 ppm) is much smaller than that of **2A** (2.70—2.01=0.69 ppm), and 3) the lower 3-H (2.70) of **2A**, which is cis to 2-COOMe, shows a small trans coupling with 4-H ($J_{3-4(trans)}$=5.3 Hz). The isomer **2B** is most likely to take an envelope conformation with two bulky substituents, 2-Me and 5-Ph, in pseudo equatorial positions. The corresponding envelope conformation of **2A** becomes less stable because the bulkier 2-Me has to occupy a pseudo axial position, the dihedral angle between 3-H (2.70) and 4-H being reduced.

Isomer **2C** has a 2,4-trans:4,5-trans structure on the basis of no shielding of 4-COOMe (δ=3.61), an NOE between one 3-H (2.16) and 2-Me, and an NOE between the other 3-H (2.74) and 4-H. Therefore, the other 4,5-trans isomer **2D** was assigned to be 2,4-cis:4,5-trans structure. Large trans couplings between the higher 3-H (2.16) and 4-H ($J_{3-4(trans)}$=11.0 Hz) and between 4-H and 5-H ($J_{4-5(trans)}$=9.9) are consistent with the assigned geometry of **2C**.

Thus, *N*-sodioazomethine ylides generated from **1** either by treating with sodium hydride or sodium iodide/triethylamine exhibited different stereoselectivities. The only differences anticipated would be 1) higher concentration of the intermediate ylide in the former case, and 2) existence of triethylammonium iodide (or together with triethylamine and sodium iodide) in the latter case.

Therefore, the *N*-sodioazomethine ylide was first generated by using sodium hydride and then treated with triethylamine (1.2 equiv). The resulting species was allowed to react with methyl acrylate. Surprisingly, the pattern of stereoselectivity changed dramatically to produce 2,4-trans:4,5-trans cycloadduct **2C** as major isomer along with 2,4-cis:4,5-trans minor isomer **2D** (Entry 2, **2C**:**2D**=6:1), no formation of either **2A**, **2B** or Michael adduct **3** being detected.

Addition of *t*-butyl alcohol or methanol (1.1—1.2 equiv), instead of triethylamine, resulted in no any deactivation of the reactive intermediate, *N*-sodioazomethine ylide; mixtures of two cycloadducts were similarly obtained (Entries 3 and 4, **2C**:**2D**=7:1). Use of water as an additive, however, furnished **2A** as the sole isomer together with Michael adduct **3** (Entry 5, **2A**:**3**=3:5). Separation of pure **2D** from the mixture with **2C** failed.

These unusual stereoselectivities of the *N*-sodioazomethine ylide in the presence of additives let us investigate further its cycloadditions with other olefinic esters. Triethylamine or *t*-butyl alcohol was employed as additive.

With methyl crotonate and triethylamine, a 7:1 mixture of two stereoisomers was obtained in a total yield of 89% (Scheme 2 and Entry 1 in Table 2). Major isomer **4A** is identical with 2,3-cis:4,5-cis cycloadduct that was previously obtained as the sole product in the lithium bromide/triethylamine-induced reaction of **1** with methyl crotonate.[1] Minor isomer **4C** was assigned to be a 2,3-trans:4,5-trans structure because of no shielding of 4-COOMe (δ=3.64), a large trans coupling of J_{4-5} (10.2 Hz),[5] and lower resonance of 2-Me (21.32, 2-Me of **4A** appears at 20.30). Addition of *t*-butyl alcohol decreased its stereoselectivity, a 2:1 mixture of **4A** and **4C** being obtained (Entry 2).

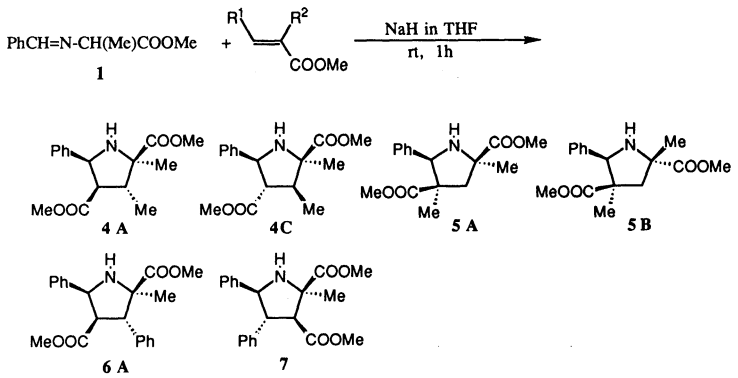
With methyl methacrylate, the reaction in the presence of triethylamine resulted in a lower isomer ratio (Entry 3, **5A**:**5B**=2.5:1) than that in the presence of *t*-butyl alcohol (Entry 4, **5A** only). The structures of **5A** and **5B** were readily determined as shown in Scheme 2 on the basis of the shielding of 4-COOMe (**5A**: δ=3.24, **5B**: 3.16) and the chemical shifts of 3-Hs (**5A**: 1.77 and 3.04, **5B**: 2.30 and 2.66).

A 1:2 mixture of two regioisomers **6A** and **7** was

Table 1. Sodium Hydride-Induced Reactions of Imine **1** with Methyl Acrylate

Entry	NaH	Additive (equivalent)	Time/h	Product (yield/%)[a]
1	1.5	None	1	**2A**(45)+**2B**(13)+**2C**(6)+**3**(25)
2	1.2	NEt_3 1.2	1	**2C**+**2D** (79) **2C**:**2D**=6:1[b,c]
3	1.2	*t*-BuOH 1.1	1	**2C**+**2D** (82) **2C**:**2D**=7:1[b,c]
4	1.2	MeOH 1.2	0.25	**2C**+**2D** (79) **2C**:**2D**=7:1[b,c]
5	1.2	H_2O 1.2	0.25	**2A**+**3** (54) **2A**:**3** =3:5[b,d]

a) Yields of isolated products. b) Determined by ^{1}H NMR of unpurified reaction mixture. c) Only **2C** could be separated by column chromatography. d) Inseparable mixture.



Scheme 2.

Table 2. Sodium Hydride-Induced Reactions of Imine **1** with Electron-Deficient Olefins[a]

Entry	Olefin	NaH Additive (equivalent)	Product (yield/%)[b]
1	Methyl crotonate	1.2 NEt_3 1.2	**4A**+**4C** (89) **4A**:**4C**=7:1[c,d]
2	Methyl crotonate	1.2 *t*-BuOH 1.1	**4A**+**4C** (79) **4A**:**4C**=2:1[c,d]
3	Methyl methacrylate	1.2 NEt_3 1.2	**5A**+**5B** (79) **5A**:**5B**=2.5:1[c,e]
4	Methyl methacrylate	1.2 *t*-BuOH 1.1	**5A** (79)
5	Methyl cinnamate	1.2 *t*-BuOH 1.1	**6A**+**7** (62) **6A**:**7** =1:2[c,f]

a) All reactions were carried out for 1 h at room temperature in THF. b) Yields of isolated products. c) Determined by ^1H NMR of unpurified mixture. d) Only **4A** was isolated. e) **5A** and **5B** could be separated by column chromatography. f) **6A** and **7** could be separated by column chromatography.

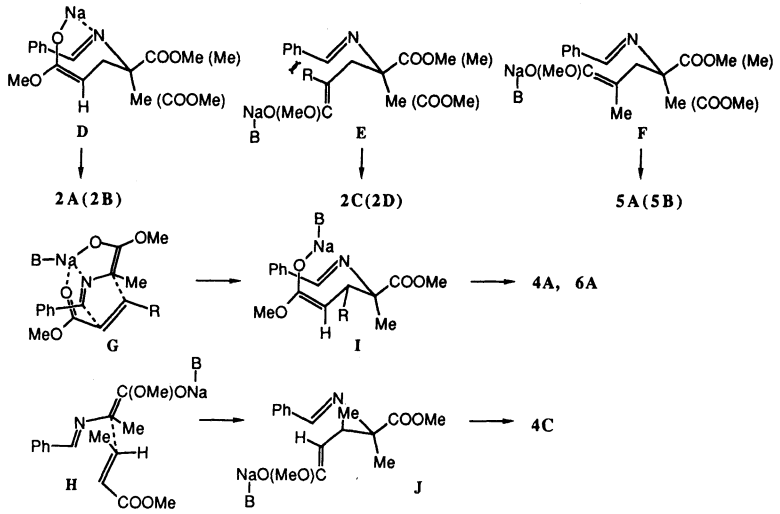


Fig. 2. Stereoselectivity in the cycloadditions of *N*-sodioazomethine ylide with esteric olefins.

obtained in the sodium hydride-induced reaction of **1** with methyl cinnamate (Entry 5). This result resembles a similar reaction induced by lithium bromide and 1,8-diazabicyclo[4.2.0]undec-7-ene (DBU) where a 2:1 mixture of **6A** and **7** was furnished in a total yield of 60%.[2]

Metal enolates containing a metal more electropositive than lithium such as sodium are most likely to undergo stepwise cycloadditions with α,β-unsaturated esters via metal enolate intermediates.[2] A concerted cycloaddition mechanism with a cyclic chelation, e.g. **B**, would be less important in these cases.

Thus, the *N*-sodioazomethine ylide of **1** reacts with methyl acrylate or methacrylate to form sodium enolate intermediates. In the reaction with methyl acrylate in the absence of additive (B), a weak interaction still working between the sodium and the imine nitrogen favors the chelation-controlled cyclization via **D** to give **2A** as major product (Fig. 2),[6] while the presence of an additive, which interacts with the

metal, not only weakens such chelation but also makes the metal bulkier. As a result, cyclization via **E** (R=H) becomes easier, the dramatic change of stereoselectivity having resulted to give **2C** as major product along with **2D**.

In the reaction of the sodium enolate intermediate from methyl methacrylate, cyclization via **E** (R=Me) becomes disfavored because these is a considerable steric repulsion between the phenyl and the methyl moieties. Thus, the cyclization via approach **F** was only observed to give **5A** and **5B**.

The Michael reaction of **1** with methyl crotonate offers an additional stereoselectivity at the newly formed bond, which finally reflects the stereochemistry of cycloadducts **4**. In the presence of a less polar additive such as triethylamine, the endo-selective cycloaddition via approach **G** (R=Me) takes place because there would still remain attractive interactions of the metal sodium to both the imine nitrogen and the ester oxygen atoms. The presence of *t*-butyl alcohol collapses the chelation **G** so that the contribution of linear transition state **H** becomes relatively more important.[7] Stereospecific cyclization of **I** and **J** leads to **4A** and **4C**, respectively.

Poor regioselectivity in the reaction of *N*-lithioazomethine ylide with methyl cinnamate is known.[2] A similar explanation would be enough for the formation of two regioisomers, **6A** and **7**.

In conclusion, 1) *N*-sodioazomethine ylides are characterized more or less as metal enolates, 2) their cycloadditions with α,β-unsaturated esters proceed through a stepwise mechanism via sodium enolate intermediates, 3) a basic additive collapses fragile metal chelations so that the stereoselectivity of cycloadditions is mainly determined by steric factors, 4) *N*-sodio ylides are synthetically complementary to other *N*-metalated ylides.

Experimental

General. Melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were taken with JASCO IRA-1 and A-702 spectrometers. ^{1}H and ^{13}C NMR spectra were recorded on JEOL FX-100 (100 MHz for ^{1}H NMR and 25.05 MHz for ^{13}C NMR) and GSX-270 (270 MHz for ^{1}H NMR and 67.94 MHz for ^{13}C NMR) instruments. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. Mass spectra and high-resolution mass spectra (HRMS) were measured with a JEOL-01SG-2 spectrometer at 70 eV of ionization energy. Elemental analyses were performed on a Hitachi 026 CHN analyzer. For preparative column chromatography, Wakogel C-200, C-300 (Wako), and Silica gel 60 (Merck) were employed. Flash chromatography was carried out on an EYELA EF-10 apparatus using a column (20×180 mm) packed with Silica gel 60 (Merck, size: 0.04—0.063 mm). Gas liquid chromatography (GLC) was accomplished on a Yanaco G-2800 gas chromatograph (Yanagimoto) with an ionization flame detector using a glass column (SE-30, 3×2000 mm) or a glass capillary column (Silicone GE, SE-30, 0.25×50000 mm). Micro vacuum distillation was carried out on a Sibata GTO-250R Kugelrohr distilling apparatus. Solvents were evaporated with a Tokyo Rikakikai rotary evaporator type-V at about 50 °C unless otherwise stated.

Materials. Dimethyl 2-methyl-*c*-5-phenyl-*r*-2,*c*-4-pyrrolidinedicarboxylate (**2A**),[1] dimethyl 2-(benzylideneamino)-2-methylpentanedioate (**3**),[2] dimethyl 2,*t*-3-dimethyl-*c*-5-phenyl-*r*-2,*c*-4-pyrrolidinedicarboxylate (**4A**),[1] dimethyl 2,*t*-4-dimethyl-*c*-5-phenyl-*r*-2,*c*-4-pyrrolidinedicarboxylate (**5A**),[1] dimethyl 2-methyl-*t*-3,*c*-5-diphenyl-*r*-2,*c*-4-pyrrolidinedicarboxylate (**6A**),[2] and dimethyl 2-methyl-*t*-4,*c*-5-diphenyl-*r*-2,*c*-3-pyrrolidinedicarboxylate (**7**)[2] were all previously prepared.

Reaction of Methyl 2-(Benzylideneamino)propanoate (1) with Sodium Hydride and Cycloaddition with Methyl Acrylate. Sodium hydride (suspension in mineral oil, 60 wt%, 0.06 g, 1.5 mmol) was washed with dry hexane (3 ml×3) and suspended in dry THF under nitrogen. Addition of imine **1** (0.191 g, 1 mmol) was followed by methyl acrylate (0.095 g, 1.1 mmol) after 5 min. The mixture was stirred at room temperature for 1 h, poured into saturated ammonium chloride (10 ml), and extracted with diethyl ether (40 ml×2). The combined extracts were dried over magnesium sulfate and evaporated in vacuo. The residue (0.261 g) was chromatographed over silica gel by using hexane–ethyl acetate (4:1 to 3:1 v/v) to give **2A** (0.125 g, 45%), **2B** (0.035 g, 13%), and **2C** (0.018 g, 6%). Formation of **3** was confirmed on the basis of ^{1}H NMR spectrum of the crude reaction mixture (25%).

Dimethyl 2-Methyl-*t*-5-phenyl-*r*-2,*t*-4-pyrrolidinedicarboxylate (2B): Colorless liquid; IR (neat) 3270, 1740, and 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.61 (3H, s, 2-Me), 2.28 (1H, dd, J_{gem}=12.8 and J_{3-4}=7.7 Hz, one of 3-H), 2.54 (1H, dd, J_{gem}=12.8 and J_{3-4}=8.2 Hz, the other of 3-H), 2.66 (1H, br, NH), 3.12 (3H, s, 4-COOMe), 3.28 (1H, ddd, J_{4-3}=8.2, 7.7, and J_{4-5}=8.8 Hz, 4-H), 3.75 (3H, s, 2-COOMe), 4.61 (1H, d, J_{5-4}=8.8 Hz, 5-H), and 7.2—7.4 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=25.44 (2-Me), 38.11 (3-C), 49.42 (4-C), 51.13, 52.42 (each COOMe), 63.80 (2-C), 65.73 (5-C), 127.31, 127.43, 127.87, 140.46 (each Ph), 173.01, and 177.75 (each COOMe); MS *m/z* (rel intensity, %) 277 (M^+, 2), 219 (15), 218 (base peak), 158 (30), and 131 (14). Found: C, 64.94; H, 6.94; N, 4.96%. Calcd for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.05%.

Dimethyl 2-Methyl-*c*-5-phenyl-*r*-2,*t*-4-pyrrolidinedicarboxylate (2C): Colorless liquid; IR (neat) 3270, 1735, and 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.53 (3H, s, 2-Me), 2.16 (1H, dd, J_{gem}=12.8 and J_{3-4}=11.0 Hz, one of 3-H, showing an NOE against 2-Me), 2.58 (1H, br, NH), 2.74 (1H, dd, J_{gem}=12.8 and J_{3-4}=7.7 Hz, the other of 3-H, showing an NOE against 4-H), 2.95 (1H, ddd, J_{4-3}=11.0, 7.7, and J_{4-5}=9.9 Hz, 4-H), 3.61 (3H, s, 4-COOMe), 3.78 (3H, s, 2-COOMe), 4.51 (1H, d, J_{5-4}=9.9 Hz, 5-H), and 7.3—7.4 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=26.54 (2-Me), 42.30 (3-C), 51.79, 52.57 (each COOMe), 52.63 (4-C), 65.33 (2-C), 66.06 (5-C), 126.92, 127.76, 128.58, 141.18 (each Ph), 173.44, and 176.98 (each COOMe); MS *m/z* (rel intensity, %) 277 (M^+, 3), 219 (15), 218 (base peak), 177 (15), 158 (32), and 131 (13). Found: C, 64.92; H, 7.01; N, 4.75%. Calcd for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.05%.

General Procedure for the Reaction of 1 with α,β-Unsaturated Esters in the Presence of Sodium Hydride and Additives. Under nitrogen, sodium hydride (60% in oil,

0.048 g, 1.2 mmol) was washed with dry hexane (3 ml×2) and suspended in dry THF (3 ml). Imine **1** (0.191 g, 1 mmol) was added, and after stirring at room temperature for 15 min was added an additive such as triethylamine (0.121 g, 1.2 mmol), *t*-butyl alcohol (0.082 g, 1.1 mmol), or water (21 mg, 1.2 mmol). After 5 min, an olefin ester (1 mmol) was added. The mixture was stirred at room temperature and then poured into saturated ammonium chloride (10 ml). Extraction with diethyl ether (40 ml×2), evaporation of the dried extract, and chromatography of the residue on silica gel gave **2—7**. The reaction conditions and results are all listed in Tables 1 and 2.

Dimethyl 2-Methyl-*t*-5-phenyl-*r*-2,*c*-4-pyrrolidinedicarboxylate (2D): This isomer could not be isolated in its pure form. Only ^{1}H NMR spectrum was recorded from the spectrum of the mixture with **2C**: ^{1}H NMR ($CDCl_3$) δ=1.50 (3H, s, 2-Me), 2.17 (1H, dd, J_{gem}=13.2 and J_{3-4}=9.9 Hz, one of 3-H), 2.30 (1H, br, NH), 2.65 (1H, dd, J_{gem}=13.2, and J_{3-4}=7.3 Hz, the other of 3-H), 2.90 (1H, ddd, J_{4-3}=9.9, 7.3, and J_{4-5}=8.4 Hz, 4-H), 3.62 (3H, s, 4-COOMe), 3.77 (3H, s, 2-COOMe), 4.47 (1H, d, J_{5-4}=8.4 Hz, 5-H), and 7.3—7.5 (5H, m, Ph).

Dimethyl 2,*c*-3-Dimethyl-*c*-5-phenyl-*r*-2,*t*-4-pyrrolidinedicarboxylate (4C): Isomer **4C** could not be separated in a pure form from the mixture with **4A**. Therefore, mixtures with two different isomer ratios were subjected to ^{1}H and ^{13}C NMR measurements, and spectra of **4C** were assigned as follows: ^{1}H NMR ($CDCl_3$) δ=1.06 (3H, d, J=7.0 Hz, 3-Me), 1.40 (3H, s, 2-Me), 2.7 (1H, br, NH), 3.64 (3H, s, 4-COOMe), 3.81 (3H, s, 2-COOMe), 4.72 (1H, d, J_{5-4}=10.2 Hz, 5-H), and 7.2—7.5 (5H, m, Ph). Both 3-H and 4-H are overlapped with the signals of **4A**. ^{13}C NMR ($CDCl_3$) δ=11.71 (3-Me), 21.32 (2-Me), 43.27 (3-C), 51.56, 52.54 (each COOMe), 56.43 (4-C), 62.33 (2-C), 68.71 (5-C), 127.11, 127.48, 127.58, 142.31 (each Ph), 172.32, and 177.46 (each COOMe).

Dimethyl 2,*c*-4-Dimethyl-*t*-5-phenyl-*r*-2,*t*-4-pyrrolidinedicarboxylate (5B): Colorless liquid; IR (neat) 3430 and 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.33 (3H, s, 4-Me), 1.60 (3H, s, 2-Me), 2.30 (1H, d, J_{gem}=13.6 Hz, one of 3-H), 2.66 (1H, d, J_{gem}=13.6 Hz, the other of 3-H), 2.70 (1H, br, NH), 3.16 (3H, s, 4-COOMe), 3.76 (3H, s, 2-COOMe), 4.06 (1H, s, 5-H), and 7.2—7.3 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=23.30 (4-Me), 25.98 (2-Me), 46.62 (3-C), 51.30, 52.38 (each COOMe), 55.09 (4-C), 64.58 (2-C), 72.83 (5-C), 126.98, 127.68, 127.87, 139.22 (each Ph), 175.20, and 178.31 (each COOMe); MS *m/z* (rel intensity, %) 291 (M^+, 5), 290 (18), 233 (17), 192 (12), 191 (89), 172 (23), 131 (64), and 130 (12). Found: C, 65.96; H, 7.54; N, 4.68%. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81%.

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4) Reaction of methyl (benzylideneamino)acetate with butyllithium resulted in no clean formation of the *N*-lithiated ylide, due to nucleophilic reactions at the ester and/or the imine moieties. This problem was solved by use of *t*-butyl ester instead of the methyl ester (S. Kanemasa and O. Uchida, unpublished results).

5) A large trans coupling of J_{4-5}=10.2 Hz can be explained only with the envelope conformation having 3-Me/4-COOMe/5-Ph all in pseudo equatorial positions. Thus, 3,4-trans:4,5-trans geometry of **4C** is confirmed.

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