

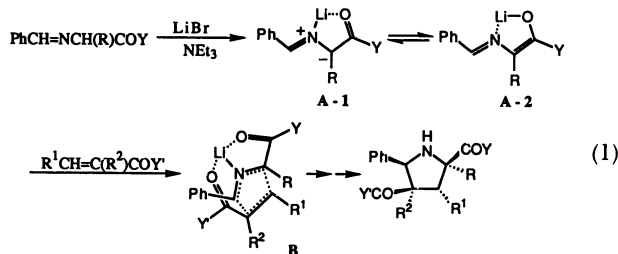
Cycloaddition vs. Michael Addition in the Metal Halide/Amine-Induced Reactions of α -(Alkylideneamino) Esters with Electron-Deficient Olefins

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The lithiated intermediate derived from methyl 2-(benzylideneamino)propanoate and lithium bromide/triethylamine undergoes cycloaddition and Michael addition with methyl acrylate. 1,3-Dipole character of the intermediate is suggested on the basis of the product ratios obtained under a variety of conditions. The reaction mechanism via a four-centered transition state is proposed.

It was found that treatment of 2-(benzylideneamino)-alkanoates or -alkanamides PhCH=NCH(R)COY ($\text{Y} = \text{OMe}$, $\text{NHBu-}t$, or 1-pyrrolidinyl; $\text{R} = \text{H}$, Me , or $i\text{-Pr}$) with lithium bromide/triethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in tetrahydrofuran (THF) led to the generation of lithiated intermediates **A** (Eq. 1).¹⁾ These species **A** showed high reactivity toward electron-deficient olefins and underwent highly stereo- and regioselective cycloadditions with α,β -unsaturated esters or ketones $\text{R}^1\text{CH=C(R}^2\text{)COY'}$ ($\text{Y}' = \text{COOMe}$, $\text{COOBu-}t$, COMe , or COAr) to produce stereochemically defined pyrrolidines.



In the preceding paper,¹⁾ we proposed two possible reaction mechanisms, concerted 1,3-dipolar cycloaddition of *N*-lithioazomethine ylide **A-1** and tandem Michael-imine addition of lithium enolate **A-2**. It was concluded that the high selectivity was due to the tight lithium chelation in the transition state, while specification of the reacting species was not made.

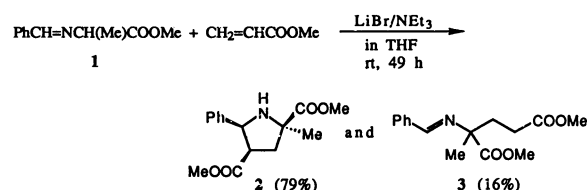
On the other hand, Michael additions with the imines of α -amino esters²⁾ or nitriles³⁾ are known. In some cases, metallic bases such as lithium diisopropylamide (LDA) and potassium *t*-butoxide were used as bases so that metalated intermediates like **A** must have been involved. Accordingly, metalated intermediates derived from the imines of α -amino esters can serve as both 1,3-dipoles and Michael donors, and probably the course of reactions depends upon the reaction conditions.

In the present article, the reaction of methyl 2-(benzylideneamino)propanoate with methyl acrylate has been investigated under various conditions employ-

ing metal halides/triethylamine or DBU. An alternative reaction mechanism leading to cycloaddition and Michael addition is presented.

Results and Discussion

An exception of the highly stereo- and regioselective cycloadditions of anions **A** depicted in Eq. 1 was the reaction of methyl 2-(benzylideneamino)propanoate (**1**) with methyl acrylate under identical conditions (with lithium bromide and triethylamine in THF at room temperature). A 5:1 mixture of cycloadduct **2** and Michael adduct **3** was produced (Scheme 1 and Entry 1 in Table 1). Therefore this reaction was investigated here under a variety of conditions. Analysis of the product ratio would help us to solve the factors which may be responsible for the determination of the reaction courses. The results are summarized in Table 1.



Scheme 1.

In most cases the reactions were carried out under the standard conditions using each 1.5 and 1.2 equivalent amounts of lithium bromide and triethylamine at room temperature in dry THF (5 ml for 1 mmol of imine **1**). The isomer ratio **2**:**3** remained unchanged (4–5:1) for several reaction times and temperatures (Entries 1–3 and 8). The comparable **2**:**3** ratio was observed even in the midst of reaction, indicating the kinetically controlled formation of both **2** and **3** (Entry 4). In fact compounds **2** and **3** were not interconverted with each other under these reaction conditions.⁴⁾

A possible reaction mechanism was illustrated on the basis of the above results and the following observations (Fig. 1). Lithium bromide coordinates

with the imine nitrogen of **1** so that the α -hydrogen of **C** can be easily deprotonated with a weak base such as triethylamine to generate lithiated intermediate **D**.

As mentioned above, two intermediates **A-1** and **A-2** ($R=Me$, $Y=OMe$) were proposed in the preceding paper.¹⁾ However the only structural difference between **A-1** and **A-2** comes from the relative covalency of the lithium-heteroatom bonds, indicating the existence of little, if any, energy barrier between them. We propose that anionic species **D** can be an intermediate which may exhibit properties both as *N*-lithiated azomethine ylide and as ester enolate.

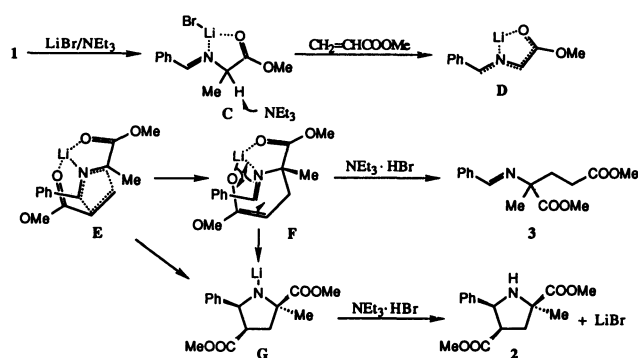


Fig. 1. Competitive formation of a cycloadduct **2** and a Michael adduct **3**.

Intermediate **D** would then be involved in the transition state **E** previously proposed for the lithium-chelated concerted cycloaddition.¹⁾ Bond formation at the β -carbon of the acrylate precedes that at the α -carbon to give **F**. Quenching of **F** with a proton source, presumably triethylammonium bromide, leading to Michael adduct **3** competes with intramolecular cyclization producing cycloadduct lithium amide **G**.⁵⁾ Ready quenching of **G** with the ammonium salt produces cycloadduct **2**. The direct formation of **G** from **E** may also be involved.

In Entries 9–13, a catalytic amount of lithium bromide and/or triethylamine was employed. Both lithium bromide and triethylamine can be effectively recycled in the manner shown in Fig. 1. Since the step of deprotonation of **1** (**C**→**D**) is rate-determining as suggested by the rate acceleration upon using DBU (Entries 22–24), the catalyzed reactions were relatively decelerated. It is not surprising that no reaction took place in the absence of lithium bromide (Entry 13).

When either lithium bromide or triethylamine was used in moderate excess, the ratio of cycloaddition increased (Entries 14, 15). Presumably the excess lithium bromide or triethylamine reduces acidity of triethylammonium bromide by coordination.

Dilution with THF increased the amount of **2** (Entries 3 and 5–7). Since collapse of **F** into **3** is an

Table 1. LiBr/Amine-Induced Reactions of Imine **1** with Methyl Acrylate

Entry	LiBr	NEt ₃ (equivalent)	DBU	H ₂ O	Temperature °C	Time h	Solvent ^{a)}	Yield/% ^{b)} 2+3	2 : 3 ^{c)}	Recovered 1 %
1	1.5	1.2			Room temp	49	THF	95	5 : 1	—
2	1.5	1.2			Room temp	3	THF	99	4 : 1	—
3	1.5	1.2			Room temp	1	THF	97	4 : 1	Trace
4	1.5	1.2			Room temp	10 min	THF	51	5 : 1	43
5	1.5	1.2			Room temp	15	THF (30 ml)	77	10 : 1	18
6	1.5	1.2			Room temp	2	THF (13 ml)	81	6 : 1	17
7	1.5	1.2			Room temp	2	THF (2.5 ml)	89	3 : 1	—
8	1.5	1.2			Reflux	1	THF	99	4 : 1	—
9	0.1	1.2			Room temp	1	THF	41	3.5 : 1	50
10	0.1	1.2			Room temp	14	THF	97	3 : 1	—
11	1.5	0.1			Room temp	3	THF	67	2.2 : 1	21
12	0.1	0.1			Room temp	48	THF	70	6 : 1	20
13	0	1.2			Room temp	20	THF	Trace	Trace	90
14	3.3	1.2			Room temp	1	THF	91	10 : 1	—
15	1.5	3.0			Room temp	1	THF	95	6 : 1	—
16	1.5	1.2		0.7	Room temp	1	THF	95	1.2 : 1	Trace
17	1.5	1.2		3	Room temp	1	THF	52	1 : 2	35
18	1.5 ^{d)}	1.2			Room temp	2	THF	95	2 : 1	—
19	1.5	1.2			Room temp	1	MeCN	79	1 : 1.4	—
20	1.5	1.2			Room temp	3	CH ₂ Cl ₂	92	1 : 3.3	—
21	1.5	1.2			Room temp	3	Et ₂ O	44	2.5 : 1	50
22	1.5		1		Room temp	1 min	THF	96	1.8 : 1	—
23	1.5		1		Room temp	2	THF (50 ml)	99	10 : 1	—
24	1.5		0.1		Room temp	5 min	THF	98	1.8 : 1	—
25	1.5		1		−78	4.5	THF	98	1 : 5	—
26	1.5		1	1	−78	4.5	THF	83	1 : 5	14

a) Unless otherwise stated, 5 ml of solvent was used for 1 mmol of **1**. The amount in parenthesis indicates the volume of THF used for 1 mmol of **1**. b) Yield of isolated mixtures. c) Based on the ¹H NMR of an isolated mixture of **2** and **3**. d) Lithium iodide was used instead of LiBr.

intermolecular reaction and the dilution procedure disfavors this process, the relative rate of intramolecular process **F**→**G** was increased as a result. The effect of only catalytic amounts of lithium bromide and triethylamine (Entry 12) is similar to that of dilution.

Addition of water results in an increase of proton source; the Michael adduct formation increased (Entries 16, 17). It should be emphasized, however, that both anions **D** and **F** are quite stable toward water. Most of them can survive upon addition of 0.7 equivalent of water which corresponds to a large excess against **D** and **G**.⁶⁾

When lithium bromide (Entry 11) or triethylamine (Entries 9, 10) was used in a large excess (twelve- or fifteen-fold equivalents) in some catalyzed reactions, the 2:3 ratio was unexpectedly decreased. The large excess lithium bromide and triethylamine presumably collapse the lithium chelation **E** which is essential for the formation of **G**.

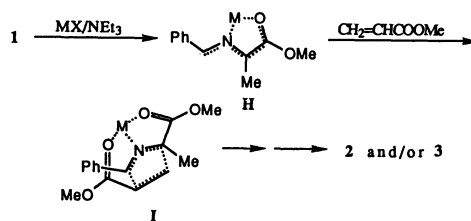
Replacement of THF by acetonitrile, dichloromethane, or diethyl ether favored the Michael addition (Entries 18–20). However the effect of polarity of solvent on 2:3 ratio remains ambiguous because all the reactions except in THF were carried out as suspension.

When DBU was employed as a stronger base, reactions were completed within 1 min at room temperature, indicating high acceleration of the deprotonation step leading to **D**. The decreased 2:3 ratio (1.8:1, Entry 21) is due to a relatively high concentration of intermediate **D** compared with the case employing triethylamine. No change of the 2:3 ratio in the DBU-catalyzed reaction (Entry 23) and predominant formation of the cycloadduct **2** in the ten-fold dilution reaction (Entry 22) are both comparable to the above results, Entries 9–11 and Entries 5, 6, respectively.

Deprotonation of **1** with lithium bromide and DBU occurred even at -78°C , but the reaction with methyl acrylate at -78°C unfortunately gave a low 2:3 ratio (Entry 24). Addition of water provided a similar result

(Entry 25).

As discussed above, the 2:3 ratio is mainly determined by the relative rate of cyclization of **F** into **G**. On the other hand, route **E**→**F** competes with the direct cyclization route **E**→**G**. Substitution of the electropositive lithium metal in the intermediate **D** with a less positive one such as aluminum or magnesium is expected to increase the relative contribution of route **E**→**G**.



Scheme 2.

With an expectation to open the entry for similar metalated intermediates **H**, other metal halides (MX) were employed in the deprotonation step of imine **1** (Scheme 2). Thus **1** was treated with a variety of metal halides and triethylamine in dry THF in the presence of methyl acrylate. Since the resulting intermediates **H** certainly undergo chelation-controlled reactions with the acrylate via **I**, cycloadduct **2** and/or Michael adduct **3** are to be formed.

The results are summarized in Table 2. Quantitative recovery of the starting imine **1** in Entries 3 and 5 is due to the extremely poor solubility of sodium bromide and potassium iodide in THF. Use of sodium iodide generated intermediate **H** (M=Na) which led to preferred formation of Michael adduct **3** (Entry 4). Magnesium bromide diethyl etherate, zinc chloride, and ethylaluminum dichloride are also effective; the cycloadduct **2** was the only identified product as expected in all cases (Entries 6–10).

Michael additions occur regioselectively at the β -carbon of the olefins bearing an anion-stabilizing substituent. On the other hand, the regioselectivity of 1,3-dipolar cycloadditions with azomethine ylides

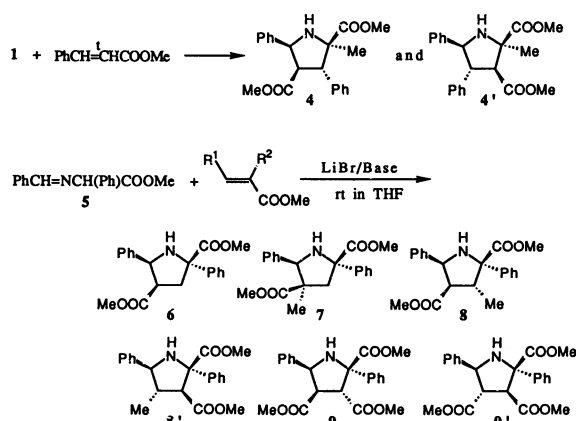
Table 2. Metal Halide/Triethylamine-Induced Reactions of Imine **1** with Methyl Acrylate^{a)}

Entry	Metal halide	Triethylamine (equivalent)	Time/h	Yield/% ^{b)}	2 : 3 ^{c)}	Recovered 1
1	LiBr	1.5	3	99	4 : 1	—
2	NaBr	1.5	8	Trace	—	98
3	NaI	1.5	8	96	1 : 2.7	—
4	KI	1.5	8	Trace	—	98
5	MgBr ₂ ^{d)}	1.5	7	99 ^{e)}	1 : 0	—
6	MgBr ₂ ^{d)}	0.2	45	99 ^{e)}	1 : 0	—
7	ZnI ₂	1.5	7	79	1 : 0	—
8	ZnI ₂	0.1	68	39	1 : 0	—
9	Et ₂ AlCl	1.5	3	99 ^{e)}	1 : 0	—

a) All reactions were carried out in dry THF at room temperature. b) Yield of the isolated mixtures. c) Based on the ¹H NMR of an isolated mixture of **2** and **3**. d) Magnesium diethyl etherate was used. e) Unidentified isomers are contained in 5 to 8% (¹H NMR).

depends upon the orbital coefficients of frontier orbitals of both reagents.⁷⁾ Accordingly, examination of regioselectivity of the above reactions is an important clue by which the reaction mechanism is solved.

The lithium chelation-controlled cycloadditions of imines of α -amino esters and amides with electron-deficient olefins offer a few exceptional selectivities as shown below. Reaction of the lithium anion of **1** with methyl cinnamate gave two cycloadducts **4** and **4'** in a 2:1 ratio (Scheme 3 and Table 3). The major product **4** was assigned as a normal stereoisomer on the basis of the chemical shifts of 2-COOMe ($\delta=3.79$), 4-COOMe (3.08), and 2-Me (1.19), while **4'** was its regioisomer (COOMe: 3.59 and 3.75; 2-Me: 1.74; 3-H: 3.31 as a doublet; 4-H: 3.75 as a doublet-doublet).



Scheme 3.

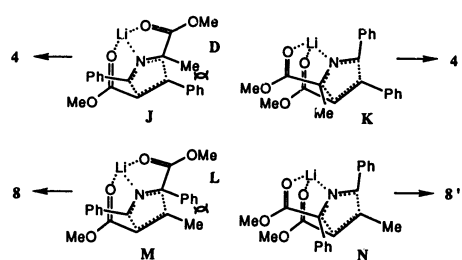


Fig. 2. Decreased regioselectivity by a steric repulsion.

Methyl 2-(benzylideneamino)phenylacetate (**5**) was reacted with several olefins in the presence of lithium bromide and triethylamine (Scheme 3 and Table 3). With methyl acrylate and methyl methacrylate normal regio- and stereoisomers **6** and **7** were obtained as single products. The reaction with methyl crotonate, however, gave two regioisomeric cycloadducts **8** and **8'** (1:6). It was quite surprising that abnormal regioisomer **8'** was the far major product. Structures of **8** and **8'** were also based on their ¹H NMR spectra: **8**: 4-COOMe: 3.21; 4-H: 3.02 as doublet-doublet; **8'**: 3-COOMe: 3.62; 3-H: 3.32 as a doublet.

In both approaches J and M leading to normal regioisomers **4** and **8**, respectively, serious steric repulsion exists between the methyl and phenyl substituents. Especially the repulsion in M should be more critical because the phenyl plane of **L** is forced out of the ylide triangle due to steric congestion caused by the adjacent methoxyl moiety.⁹⁾ Substitution by a phenyl moiety at the β -carbon of acrylate causes a decrease of the coefficient of the lowest unoccupied molecular orbital (LUMO) at this position. The reported atomic orbital coefficients (LUMO) are as follows:⁹⁾ methyl acrylate: C(C _{α}): 0.4286; C(C _{β}): -0.6194. Methyl cinnamate: C(C _{α}): 0.4717; C(C _{β}): -0.4248. This may be the reason why the regioisomeric approach K has participated in cycloaddition to give **4'**.

The unexpected regioselectivity giving **8'** as a far major regioisomer should be due to the serious steric repulsion in approach M which was already mentioned above. Predominant formation of **9'** in the reaction of **5** with dimethyl fumarate stems from a similar steric repulsion.

The above anomalous regiochemical consequences support the cycloaddition transition state, for example E, of anionic intermediate such as D or H first proposed in the present work.

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

Table 3. LiBr/Amine-Induced Reactions of Imine **1** or **5** with Electron-Deficient Olefins^{a)}

Entry	Imine	Olefin	LiBr (equivalent)	Amine	Time/h	Product	Yield/(%) ^{b)}	Isomer ratio
1	1	Methyl crotonate	1.5	DBU 1	4	4+4'	60 (—)	4:4' =2:1 ^{c)}
2	5	Methyl acrylate	1.5	NEt ₃ 1.2	8	6	81 (8)	
3	5	Methyl methacrylate	1.5	NEt ₃ 1.2	15	7	46 (40)	
4	5	Methyl methacrylate	1.5	DBU 1	1	7	96 (—)	
5	5	Methyl crotonate	1.5	NEt ₃ 1.2	4	—	0 (100)	
6	5	Methyl crotonate	1.5	DBU 1	1	8+8' ^{d)}	67 (—)	8:8' =1:6 ^{e)}
7	5	Dimethyl fumarate	1.5	DBU 1	3	9+9' ^{d)}	82 (—)	9:9' =1:5 ^{e)}

a) All reactions were carried out in dry THF at room temperature. b) Yield of the isolated product(s). Yield of unreacted **5** is in parenthesis. c) Both isomers were separated from each other. The ratio was determined by ¹H NMR of the unpurified product. d) As an inseparable mixture. e) Based on ¹H NMR of the unpurified mixture.

spectrometer. ^1H NMR spectra were recorded on a Hitachi R-40 (90 MHz), a JEOL FX-100 (100 MHz), or a JEOL GSX-270 instrument (270 MHz), and ^{13}C NMR on a JEOL FX-100 (25.05 MHz) or a JEOL GSX-270 spectrometer (67.94 MHz). 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 $\times$ 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 $\times$ 2000 nm) or a glass capillary column (Silicone GE, SE-30, 0.25 $\times$ 50000 mm). Micro vacuum distillation was carried out on a Sibata GTO-250R Kugelrohr distilling apparatus.

General Procedures for Metal Halide/Amine-Induced Reactions of Imine 1^{b} or 5^{10} with Electron-Deficient Olefins. To a solution of imine **1** or **5** in dry THF (or other solvent) was added a metal halide under nitrogen. Addition of an olefin was followed and then an amine, both with the aid of a syringe. If necessary, an additive was added and the resulting mixture was stirred under the reaction conditions listed in Tables 1–3. After the reaction was over, the mixture was treated with saturated ammonium chloride and extracted with diethyl ether. The extract was dried over magnesium sulfate and evaporated in vacuo. The residue was subjected to ^1H NMR measurement to know the purity of products as well as the isomer ratio.

Dimethyl 2-(Benzylideneamino)-2-methylglutarate (3):

This compound **3** decomposed so readily when chromatographed on silica gel that its separation from the mixture with 2^{b} was unsuccessful. **3:** Colorless liquid; IR (neat) 1730 (C=O) and 1630 (C=N) cm^{-1} ; ^1H NMR (CDCl_3) δ =1.49 (3H, s, Me), 1.9–2.6 (4H, m, CH_2), 3.60, 3.69 (each 3H, s, COOMe), 7.3–7.4 (3H, m, Ph), 7.7–7.8 (2H, m, Ph), and 8.24 (1H, s, CH=N); MS m/z (rel intensity, %) 278 ($\text{M}^+ + 1$, 2), 219 (17), 218 (base peak), 158 (47), 131 (19), 130 (19), 104 (34), 98 (53), 90 (28), and 89 (19). No HRMS was obtainable due to the lack of M^+ .

Dimethyl 2-Methyl-*t*-3,*c*-5-diphenylpyrrolidine-*r*-2,*c*-4-dicarboxylate (4): The mixture of **4** and **4'** was chromatographed on silica gel by using hexane–ethyl acetate (5:1 v/v) to give **4** and then **4'**. **4:** Colorless prisms (chloroform–hexane); mp 84–85 $^\circ\text{C}$; IR (KBr) 3330 (NH), 1735, and 1720 (each C=O) cm^{-1} ; ^1H NMR (CDCl_3) δ =1.19 (3H, s, 2-Me), 3.06 (1H, br s, NH), 3.08 (3H, s, 4-COOMe), 3.79 (3H, s, 2-COOMe), 3.91 (1H, dd, J_{4-3} =10.6 and J_{4-5} =9.5 Hz, 4-H), 4.20 (1H, d, J_{3-4} =10.6 Hz, 3-H), 4.90 (1H, d, J_{5-4} =9.5 Hz, 5-H), 7.2–7.4 (8H, m, Ph), and 7.44 (2H, d, Ph); ^{13}C NMR (CDCl_3) δ =21.22 (2-Me), 51.32, 52.44 (each COOMe), 54.44, 54.98 (3- and 4-C), 62.81 (5-C), 68.87 (2-C), 127.30, 127.38, 127.77, 128.19, 128.28, 128.64, 137.22, 140.34 (each Ph), 171.69, and 175.50 (each COOMe); MS m/z (rel intensity, %) 353 (M^+ , 1), 295 (18), 294 (83), 234 (31), 192 (16), 191 (base peak), 132 (13), 131 (92), 130 (17), 115 (18), 103 (11), 91 (17), 90 (16), and 77 (10). Found: C, 71.18; H, 6.55; N, 4.00%. Calcd for $\text{C}_{21}\text{H}_{23}\text{NO}_4$: C, 71.37; H, 6.56; N, 3.96%.

Dimethyl 2-Methyl-*t*-4,*c*-5-diphenylpyrrolidine-*r*-2,*c*-3-dicarboxylate (4'): Colorless needles (chloroform–hexane); mp 108–109 $^\circ\text{C}$; IR (KBr) 3360 (NH), 1735, and 1717 (C=O) cm^{-1} ; ^1H NMR (CDCl_3) δ =1.74 (3H, s, 2-Me), 3.03 (1H, br s, NH), 3.31 (1H, d, J_{3-4} =12.1 Hz, 3-H), 3.59 (3H, s, 3-COOMe), 3.63 (1H, dd, J_{4-3} =12.1 and J_{4-5} =10.6 Hz, 4-H), 3.75 (3H, s, 2-COOMe), 4.31 (1H, d, J_{5-4} =10.6 Hz, 5-H), and 7.1–7.3 (10H, m, Ph); ^{13}C NMR (CDCl_3) δ =27.37 (2-Me), 51.98, 52.76 (each COOMe), 57.33 (3-C), 63.18 (4-C), 67.87, 69.12 (2- and 5-C), 127.05, 127.27, 127.61, 127.71, 128.43, 128.51, 138.02, 140.13 (each Ph), 171.77, and 175.19 (each COOMe); MS m/z (rel intensity, %) 294 ($\text{M}^+ - \text{COOMe}$, 28), 192 (11), 191 (87), 132 (13), 131 (base peak), 130 (23), 129 (17), 128 (10), 115 (16), 91 (17), 90 (17), and 77 (10). Found: C, 71.35; H, 6.61; N, 4.02%. Calcd for $\text{C}_{21}\text{H}_{23}\text{NO}_4$: C, 71.37; H, 6.56; N, 3.96%.

Dimethyl 2,*c*-5-Diphenylpyrrolidine-*r*-2,*c*-4-dicarboxylate (6): Colorless needles (chloroform–hexane); mp 104–105 $^\circ\text{C}$; IR (KBr) 3360 (NH), 1735, and 1730 (C=O) cm^{-1} ; ^1H NMR (CDCl_3) δ =2.61 (1H, dd, J_{gem} =13.2 and J_{3-4} =7.0 Hz, one of 3-H), 3.15 (1H, dd, J_{gem} =13.2 and J_{3-4} =5.9 Hz, the other of 3-H), 3.22 (3H, s, 4-COOMe), 3.23 (1H, ddd, J_{4-5} =7.3 and J_{4-3} =7.0 and 5.9 Hz, 4-H), 3.48 (1H, br s, NH), 3.75 (3H, s, 2-COOMe), 4.57 (1H, d, J_{5-4} =7.3 Hz, 5-H), 7.3–7.4 (8H, m, Ph), and 7.74 (2H, d, Ph); ^{13}C NMR (CDCl_3) δ =40.99 (3-C), 50.32 (4-C), 51.16, 52.81 (each COOMe), 64.74 (5-C), 71.83 (2-C), 126.33, 126.75, 127.48, 127.64, 128.23, 128.33, 139.22, 143.08 (each Ph), 173.05, and 174.48 (each COOMe); MS m/z (rel intensity, %) 281 (20), 280 ($\text{M}^+ - \text{COOMe}$, base peak), 220 (27), 193 (27), 115 (17), 104 (11), and 76 (11). Found: C, 70.86; H, 6.30; N, 4.02%. Calcd for $\text{C}_{20}\text{H}_{21}\text{NO}_4$: C, 70.78; H, 6.24; N, 4.13%.

Dimethyl *t*-4-Methyl-2,*c*-5-diphenylpyrrolidine-*r*-2,*c*-4-dicarboxylate (7): Colorless prisms (chloroform–hexane); mp 114–115 $^\circ\text{C}$; IR (KBr) 3360 (NH), 1720, and 1710 (C=O) cm^{-1} ; ^1H NMR (CDCl_3) δ =1.24 (3H, s, 4-Me), 2.31 (1H, d, J_{gem} =13.6 Hz, one of 3-H), 3.31 (3H, s, 4-COOMe), 3.37 (1H, d, J_{gem} =13.6 Hz, the other of 3-H), 3.76 (3H, s, 2-COOMe), 3.82 (1H, br s, NH), 4.02 (1H, s, 5-H), 7.2–7.4 (8H, m, Ph), and 7.76 (2H, d, Ph); ^{13}C NMR (CDCl_3) δ =21.28 (4-Me), 50.83 (3-C), 51.33, 52.84 (each COOMe), 56.34 (4-C), 71.30 (2-C), 73.33 (5-C), 126.45, 126.48, 127.32, 128.07, 128.28, 128.35, 137.45, 144.59 (each Ph), 175.01, and 175.27 (each COOMe); MS m/z (rel intensity, %) 353 (M^+ , 1), 294 (18), 293 (87), 252 (40), 233 (30), 194 (19), 193 (base peak), 129 (11), 115 (13), 104 (14), 91 (18), 90 (15), 89 (11), 77 (15), and 44 (10). Found: C, 71.52; H, 6.56; N, 4.08%. Calcd for $\text{C}_{21}\text{H}_{23}\text{NO}_4$: C, 71.37; H, 6.56; N, 4.08%.

Dimethyl *t*-3-Methyl-2,*c*-5-diphenylpyrrolidine-*r*-2,*c*-4-dicarboxylate (8) + Dimethyl *t*-4-Methyl-2,*c*-5-diphenylpyrrolidine-*r*-2,*c*-3-dicarboxylate (8'): An inseparable mixture of **8** and **8'** (1:6 by ^1H NMR) was obtained after column chromatographic purification of the crude reaction mixture on silica gel with chloroform. Spectral data were obtained as a mixture. **8:** ^1H NMR (CDCl_3) δ =0.82 (3H, d, $J_{\text{Me-3}}$ =6.6 Hz, 3-Me), 3.02 (1H, dd, J_{4-3} =10.2 and J_{4-5} =9.2 Hz, 4-H), 3.21 (3H, s, 4-COOMe), 3.40 (2H, m, 3-H and NH), 3.78 (3H, s, 2-COOMe), 5.01 (1H, d, J_{5-4} =9.2 Hz, 5-H), and 7.3–7.5 (10H, m, Ph); ^{13}C NMR (CDCl_3) δ =15.35 (3-Me), 41.11 (3-C), 51.14, 52.47 (each COOMe), 55.72 (4-C), 62.53 (5-C), 74.25 (2-C), 126.62, 127.17, 127.56, 128.07, 128.13, 128.69, 140.79, 142.00 (each Ph), 171.41, and 174.00 (each COOMe). **8':**

^1H NMR (CDCl_3) δ =0.89 (3H, d, $J_{\text{Me-4}}$ =6.6 Hz, 4-Me), 2.53 (1H, tq, J_{4-3} = J_{4-5} =9.5 and $J_{4-\text{Me}}$ =6.6 Hz, 4-H), 3.32 (1H, d, J_{3-4} =9.5 Hz, 3-H), 3.40 (1H, br s, NH), 3.61 (1H, d, J_{5-4} =9.5 Hz, 5-H), 3.62 (3H, s, 4-COOMe), 3.78 (3H, s, 2-COOMe), 7.3–7.5 (8H, m, Ph), and 7.81 (2H, d, Ph); ^{13}C NMR (CDCl_3) δ =15.55 (4-Me), 49.00 (4-C), 52.18, 52.91 (each COOMe), 64.25 (3-C), 69.07 (5-C), 74.25 (2-C), 127.08, 127.34, 127.63, 127.87, 128.25, 128.69, 140.23, 142.93 (each Ph), 173.11, and 173.93 (each COOMe).

Trimethyl 2,6-5-Diphenylpyrrolidine-*r*-2,3,4-tricarboxylate (9) + Trimethyl 2,6-5-Diphenylpyrrolidine-*r*-2,3,4-tricarboxylate (9'): An inseparable mixture of **9** and **9'** (1:5 by ^1H NMR) was obtained after column chromatographic purification of the crude reaction mixture on silica gel with chloroform. Spectral data were obtained as a mixture. **9**: ^1H NMR (CDCl_3) δ =3.25, 3.34 (each 3H, s, 3- and 4-COOMe), 3.6–3.9 (2H, m, 4-H and NH), 3.80 (3H, s, 2-COOMe), 4.54 (1H, d, J_{3-4} =7.3 Hz, 3-H), 5.15 (1H, d, J_{5-4} =8.0 Hz, 5-H), 7.2–7.6 (8H, m, Ph), and 7.85 (2H, d, Ph); ^{13}C NMR (CDCl_3) δ =52.40, 52.67, 52.76 (each COOMe), 54.47 (4-C), 61.90 (3-C), 67.95 (5-C), 74.67 (2-C), 126.79, 126.88, 127.67, 127.83, 128.68, 129.00, 139.78, 139.89 (each Ph), 171.05, 171.36, and 173.30 (each COOMe). **9'**: ^1H NMR (CDCl_3) δ =3.47 (1H, dd, J_{4-5} =9.2 and J_{4-3} =8.4 Hz, 4-H), 3.51, 3.65 (each 3H, s, 3- and 4-COOMe), 3.73 (1H, br s, NH), 3.78 (3H, s, 2-COOMe), 4.09 (1H, d, J_{3-4} =8.4 Hz, 3-H), 4.31 (1H, d, J_{5-4} =9.2 Hz, 5-H), 7.3–7.5 (8H, m, Ph), and 7.80 (2H, d, Ph); ^{13}C NMR (CDCl_3) δ =52.11, 52.51, 53.03 (each COOMe), 57.18 (4-C), 59.60 (3-C), 64.98 (5-C), 74.97 (2-C), 127.11, 127.99, 128.07, 128.19, 128.38, 128.78, 139.54, 140.95 (each COOMe), 171.82, 172.33, and 173.08 (each COOMe).

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