  Bull. Chem. Soc. Jpn., 58, 3320—3336 (1985) [Vol. 58, No. 11

Stereochemical Study on 1,3-Dipolar Cycloaddition Reactions of Heteroaromatic *N*-Ylides with Unsymmetrically Substituted Olefinic Dipolarophiles

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(Received July 8, 1985)

Regioselectivity and stereoselectivity of the cycloadditions of heteroaromatic *N*-ylides with unsymmetrically-substituted olefins such as methyl-substituted cis olefins, an acrylate, the related olefins, trans nitro olefins, and other trans olefins have been investigated. These cycloadditions are highly regioselective, while the stereoselectivity depends upon both the electronic and steric nature of substituents of the ylide and olefin. The 1-endo-2-exo cycloadducts of the anti form of ylides which have been formed as kinetically controlled products undergo the isomerization into either the 1-endo-2-exo cycloadducts of the syn ylides through a retro cycloaddition process or the 1-exo-2-endo cycloadducts of the syn ylides *via* betaine intermediates.

The preceding paper has dealt with the stereochemical study on the 1,3-dipolar cycloaddition reactions of heteroaromatic *N*-ylides to symmetrically substituted cis and trans olefins,[1] and some important stereochemical features in such cycloadditions have been figured out:

1) The anti form of ylides exclusively participates in the cycloadditions if the ylides are stabilized by a substituent of carbonyl type.

2) The reactions with cis olefins are highly stereoselective, the endo approach of olefins to the anti ylides being the only favored pathway.

3) If the cycloadducts formed are substituted by strongly electron-withdrawing groups, they suffer from the ready stereospecific dissociation into the starting ylides and olefins which then recombine in a stereospecific manner giving the thermodynamically more favored isomers.

4) After all, the stereochemical course of cycloadditions of heteroaromatic *N*-ylides depends upon the electronic nature and steric size of substituents on the olefins and ylides. The attractive secondary orbital interaction working between the olefin substituents and the heteroaromatic plane leads to the kinetically favored cycloadducts, and the steric repulsion working among the olefin substituents and the ylide ring and substituent favors the formation of thermodynamically controlled cycloadducts. The stereochemistry of the reactions is revealed as a result from the counter-balance of the above two interactions.

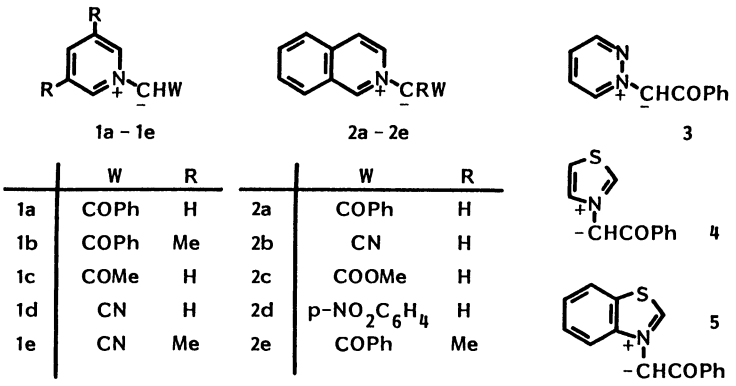
In the present paper, the cycloaddition reactions of heteroaromatic *N*-ylides to unsymmetrically substituted cis and trans olefins are investigated with the aim of knowing the generality and limitation of our rules which were outlined in the preceding paper and abstracted above. In the reactions with unsymmetrical olefins, of special interest are the regioselectivity, the stereoselectivity of ylide substituent (or the periselectivity), the stereoselectivity of olefin substituents (the endo and exo selectivity), and the thermodynamical stability of cycloadducts. For wide applications of the 1,3-dipolar cycloadditions to organic synthesis, it is necessary to discriminate among the factors which control the stereochemistry of cycloaddition and to understand which certain factor predominates over the other.

So far examples for the cycloadditions of heteroaromatic *N*-ylides to unsymmetrically substituted olefinic dipolarophiles are quite limited. In the most reported cases, the cycloadducts could not be isolated because of their instability[2] or, if isolated, their stereostructures remained unsolved.[3,4] It is only in recent year that the regio- and stereoselective cycloadducts of triazolium or dihydroisoquinolinium methylides to acrylic olefins have been reported to be the endo cycloadducts to the anti form of the ylides.[5,6] Some other unsymmetrical olefins have been employed in the cycloadditions to dihydroisoquinolinium methylides giving the regio- and stereoselective cycloadducts with a cis-trans-cis geometry as to the newly formed five-membered rings.

Results and Discussion

Thirteen heteroaromatic *N*-ylides **1**—**5** including five different types of heterocyclic systems were employed in the present work as shown in Scheme 1: Several pyridinium methylides **1a**—**e**, isoquinolinium methylides **2a**—**e**, pyridazinium **3**, thiazolium **4**, and benzothiazolium phenacylides **5**. These ylides are labile, so they were all generated *in situ* from the corresponding quaternary bromides and triethylamine in the presence of an olefinic dipolarophile.

After the cycloaddition was completed, triethylamine hydrobromide quantitatively formed was removed off by washing the reaction mixture with water. The crude mixture was submitted, in every case, to the ^{1}H-NMR measurement to get informations on the regio- and stereoselectivity of the



	W	R
1a	COPh	H
1b	COPh	Me
1c	COMe	H
1d	CN	H
1e	CN	Me

	W	R
2a	COPh	H
2b	CN	H
2c	COOMe	H
2d	p-$NO_2C_6H_4$	H
2e	COPh	Me

Scheme 1.

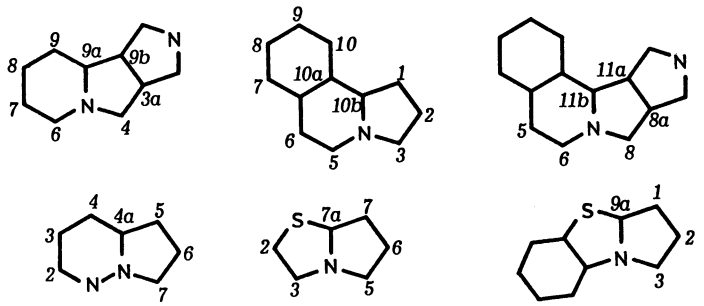


Fig. 1. Numberings for the cycloadducts formed in the reaction of heteroaromatic *N*-ylides to unsymmetrically substituted olefins.

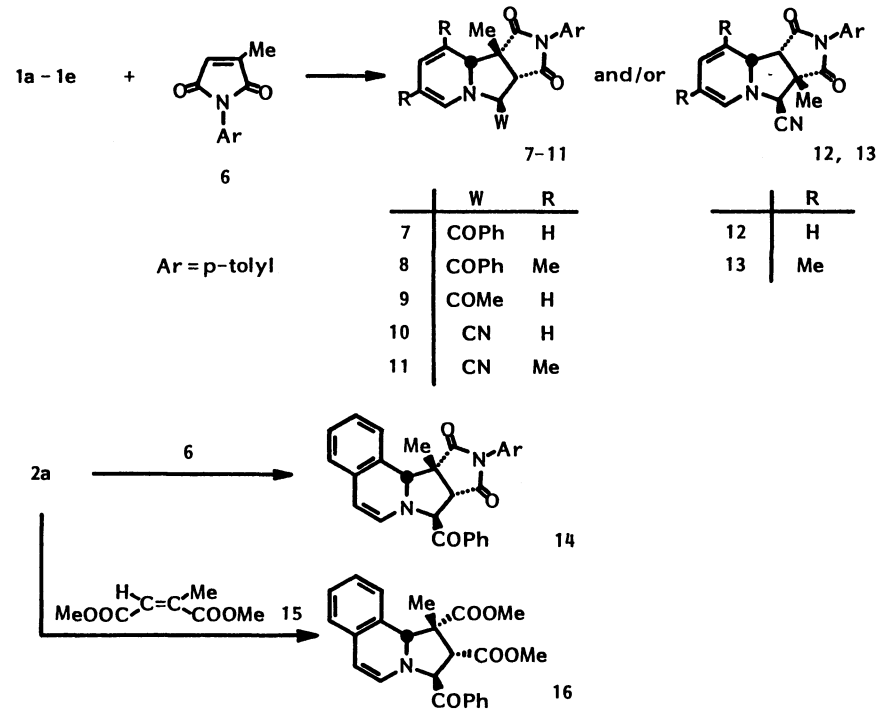
cycloaddition, and then subjected to the isolation and purification procedure of products. Figure 1 shows the numberings for the ring systems of cycloadducts formed from the cycloadditions.

Cycloadditions to Methyl-substituted cis Olefins. We have recently found that such cis olefins as maleimides and maleates undergo the stereospecific and stereoselective cycloadditions to heteroaromatic *N*-ylides providing the endo 3+2 cycloadducts to the anti form of ylides.[1] When a methyl substituent is introduced at the olefin part of cis olefins, one of two possible endo approaches between the ylide and the methyl-substituted cis olefin may be disfavored because of the steric repulsion between the methyl moiety and a ylide-stabilizing substituent. Therefore, it is easily expected that the regioselectivity of cycloadditions to methyl-substituted cis olefins should be excellent in favor for the formation of cycloadducts with the methyl and ylide-stabilizing substituents in a 1,3-relationship.

The reaction of pyridinium phenacylide **1a** with *N*-(*p*-tolyl)citraconimide **6** in chloroform at room temperature produced a single isomer of the 3+2 cycloadduct **7** in a quantitative yield as shown in Scheme 2 and Table 1. Similarly 3,5-dimethylpyridinium phenacylide **1b** and pyridinium acetonylide **1c** gave almost quantitative yields of stereospecific, regio-, and stereoselective cycloadducts **8** and **9**, respectively, both as single isomers.

Although these cycloadducts **7**—**9** are all too unstable to be purified by recrystallization or column chromatography as is usual with the cycloadducts of heteroaromatic *N*-ylides to maleimides,[1] their structures were successfully determined as the 9b-methyl derivatives of the endo 3+2 cycloadducts of **6** to the anti form of **1** on the basis of the spectral data shown in Table 2. With the cycloadduct **7** as an example, the small coupling constant of 0.8 Hz between 3a-H and 4-H as well as the low field shift of 9-H compared with 7-H (5.49 and 4.82 ppm, respectively) is consistent with the endo cycloadduct to the anti ylide. It is clear that the methyl substituent is sitting at the 9b-position on the basis of the splitting patterns of methine hydrogens on the newly formed five-membered ring.

On the other hand, the reactions of pyridinium methylides **1d** and **1e** with a cyano moiety as a sterically small ylide-stabilizing substituent furnished each two regioisomeric cycloadducts **10**+**12** and **11**+**13**, respectively, whose separation was unsuccessful. The major products **12** and **13** were assigned as the 3a-methyl-substituted cycloadducts and the minor ones **10** and **11** the 9b-methyl derivatives by the careful reading of the ^{1}H-NMR spectral data. Such reversal of regioselectivity which should be deeply related with the steric size of the cyano moiety will be discussed later. The cycloadditions of isoquinolinium phenacylide **2a** to **6** and of **2a** to dimethyl citraconate



Scheme 2.

Table 1. Cycloadditions to citraconimide **6** and citraconate **15**

Ylide	Olefin	Reaction conditions[a]		Product[b]	Mp θ_m/°C	Yield/%[c]
		Temperature	Time/h			
1a	**6**	rt	11	**7**	105—107	100
1b	**6**	rt	2	**8**	145—147	100
1c	**6**	rt	13	**9**	82—85	94
1d	**6**	rt	38	**10**+**12**	d)	100 **10** : **12**=1 : 2
1e	**6**	rt	19	**11**+**13**	d)	100 **11** : **13**=1 : 3
2a	**6**	rt	10 min	**14**	98—99	100
2a	**15**	reflux	20 min	**16**	oil	100

a) Solvent: chloroform. b) All yellow to pale yellow solid. c) All isolated yields. The isomer ratio was determined by the ^{1}H-NMR spectrum. d) Melting point was not taken.

15 took place, quite readily under milder conditions than the others, giving quantitative yields of regio- and stereoselective cycloadducts **14** and **15**, respectively.

The regioselectivity in the cycloadditions with such methyl-substituted cis olefins as **6** and **15** can be satisfactorily explained by the steric repulsion during the approach of the both reagents (Fig. 2). As has been demonstrated in the preceding work,[1] the cycloadditions of heteroaromatic *N*-ylides to a variety of cis olefins proceed through the endo approach to the anti form of ylides due to both the high stabilization of anti ylide and the minimization of steric repulsion from the ylide-stabilizing substituent. The same mode of approach may be applied to the present cases. Simple combination of the polarized structures of **1** and **6** leads to the approach **A** in

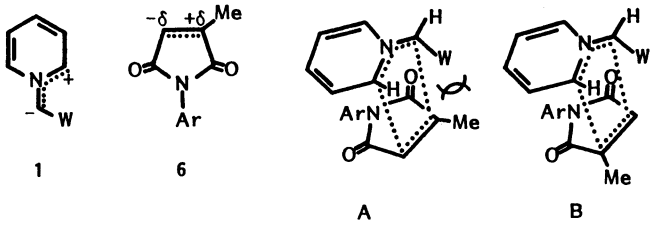


Fig. 2. Two regioisomeric endo approaches between **1** and **6**.

which some steric repulsion exists between the ylide-stabilizing substituent W and the methyl moiety. When W is small in size such as cyano group, the approach **A** is more favored providing **12** and **13** as major products. When the steric repulsion of W to the methyl is critical, the approach **A** becomes

Table 2. Spectral data for the cycloadducts to citraconic imide **6** and ester **15**

	IR (cm^{-1})	^{1}H-NMR Spectra measured in deuteriochloroform (δ, ppm, and Hz)											M$^+$ (m/z)
		4-H	3a-H	9b-H	9a-H	9-H	8-H	7-H	6-H	J_{4-3a}	J_{9b-9a}		
7	1780, 1700, 1680, 1640	5.44 d	3.68 d	Me	4.17 dd	5.49 ddt	5.95 ddt	4.82 ddd	6.13 dt	0.8	—	1.53^s(9b-Me), 2.37^s(p-Me)	a)
						4.0	10.0	6.0	7.5				
8		5.20 s	3.61 s	Me	3.77 s	Me —	5.64 br. s —	Me —	5.82 br. s —	0	—	1.60^s(7-Me), 1.66^s(9b-Me), 1.89^s(9-Me), 2.37^s(p-Me)	a)
9	1780, 1720, 1710	4.50 s	3.58 s	Me	3.94 dd	5.44 ddt	4.93 ddt	4.76 ddd	5.02 dt	0	—	1.40^s(9b-Me), 2.28^s(p-Me)	a)
						4.0	10.0	6.0	7.5				
10	2250, 1720, 1710[c]	b)	3.24 s	Me	4.45 dd	b)	b)	b)	b)	0	—	1.61^s(9b-Me), 2.37^s(p-Me)	
12		4.78 s	Me	3.10 d	b)	b)	b)	b)	b)	—	8.0	1.69^s(3a-Me), 2.37^s(p-Me)	
11	2250, 1770, 1720, 1680[c]	4.88 s	3.25 s	Me	4.25 s	Me —	5.47 br. s —	Me —	5.70 br. s —	0	—	1.55^s(7-Me), 1.61^s(9b-Me), 1.98^s(9-Me), 2.32^s(p-Me)	
13		4.80 s	Me	3.97 d	4.64 d	Me —	5.47 br. s —	Me —	5.70 br. s —	—	8.0	1.55^s(7-Me), 1.71^s(3a-Me), 1.93^s(9-Me), 2.32^s(p-Me)	
		8-H	8a-H	11a-H	11b-H			5-H	6-H	J_{8-8a}	$J_{11a-11b}$		
14	1770, 1700	5.48 d	3.80 d	Me	4.35 s			5.43 d	6.13 d	1.0	—	1.65^s(11a-Me), 2.30^s(p-Me)	448
									7.7				
		3-H	2-H	1-H	10b-H			6-H	5-H	J_{3-2}	J_{1-10b}		
16	1740—1720, 1620, 1600	5.65 d	3.68 d	Me	4.57 s			5.05 d	6.11 d	6.5	—	1.67^s(1-Me), 3.35^s, 3.64^s (1- and 2-COOMe)	405
									7.8				

a) No parent ion peak was observed. b) Could not be assigned because of the signal overlapping. c) Measured as mixtures of regioisomers.

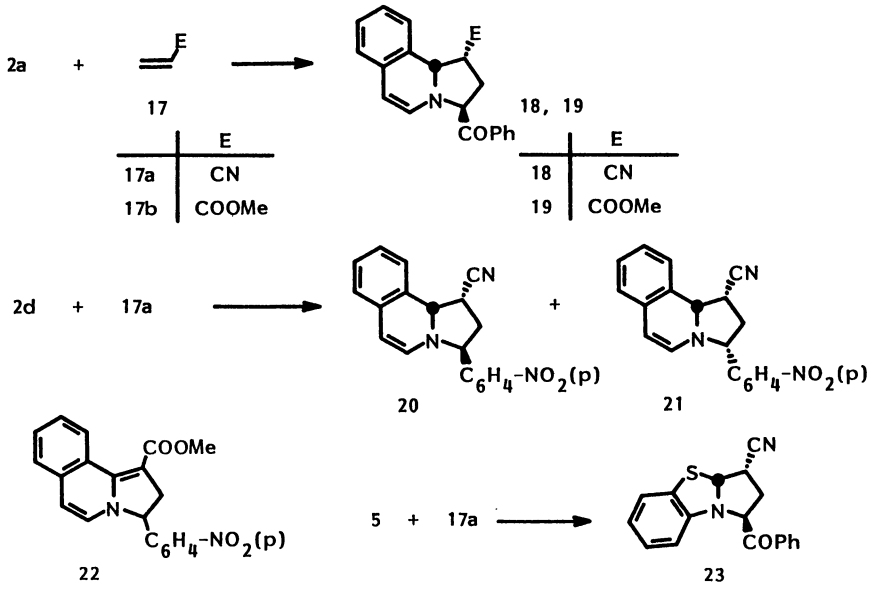
disfavored and instead the other approach **B** is the only allowed pathway.

Cycloadditions to Acrylic and Related Olefins. The cycloadditions of **2a** with acrylonitrile **17a** and methyl acrylate **17b** as monosubstituted olefinic dipolarophiles were found to occur readily, at room temperature for 10 min, furnishing quantitaive yields of regioselective and stereochemically pure 3+2 cycloadducts **18** and **19**, respectively (Scheme 3 and Table 3). On the other hand, the isoquinolinium ylide **2d** having *p*-nitrophenyl moiety as a ylide-stabilizing substituent showed very poor stereoselectivity in the reaction with **17a**, a mixture of two stereoisomers **20** and **21** being obtained in 100% yield. They were tentatively assigned as the endo 3+2 cycloadducts to the anti and syn forms of the ylide **2d** on the ground of the mechanistic discussion described later. Unfortunately the similar reaction of **2d** with **17b** gave no 3+2 cycloadduct but the only obtained product **22** was the dehydrogenated cycloadduct, 1-methoxycarbonyl-3-(*p*-nitrophenyl)-2,3-dihydropyrrolo[2,1-*a*]isoquinoline.

Although quite sluggish, the cycloaddition of benzothiazolium *N*-pnenacylide **5** to **17a** gave 74% of the regio- and stereoselective cycloadduct **23** as a single product.

The structures of these cycloadducts were confirmed mainly on the basis of the ^{1}H-NMR spectral data listed in Table 4. The cycloadduct **19** which was obtained from **2a** and **17b** offers the most clear ^{1}H-NMR spectrum supporting the proposed stereostructure as shown in Fig. 3.

The ester methyl at the 1-position, appeared at 3.28 ppm, should be sitting in the midst of shielding zone of the fused benzene ring, and hence the relationship between 1-H and 10b-H is cis. The 1-H couples with one (Ha) of two adjacent methylene hydrogens with a small coupling constant of 2.3 Hz and the other (Hb) with a medium coupling of 8.0 Hz, indicating that Ha and Hb are trans and cis to 1-H, respectively. The molecular model for **19** with a confirmed stereochemistry at the 10b-, 1-, and 2-



Scheme 3.

Table 3. Cycloaddition to acrylic **17** and related olefins **24**, **26**

Ylide	Olefin	Reaction conditions		Time/h	Product	Mp θ_m/°C	Yield/%[b]
		Solvent[a]	Temperature				
2a	**17a**	CF	rt	10 min	**18**	156—157	100
2a	**17b**	CF	rt	10 min	**19**	105—108	100
2d	**17a**	AN	rt	20 min	**20**+**21**[c]	oil	100
2d	**17b**	CF+AN[d]	rt	2	**22**	oil	60
5	**17a**	CF	rt	3	**23**	129—130	74
2d	**24**	AN	rt	2	**25**	oil	100
2a	**26**	CF	rt	10 min	**27**	73—76	100

a) CF: chloroform; AN: acetonitrile. b) All isolated yields. c) The isomer ratio could not be determined. d) chloroform: acetonitrile=25 : 1.

Table 4. Spectral data for the cycloadducts to acrylic **17** and related olefins **24**, **26**

	IR (cm^{-1})	^{1}H-NMR Spectra (δ, ppm, and Hz)[a]							M$^+$(m/z)
		3-H	2-Ha[b]	2-Hb[c]	1-H	10b-H	6-H	5-H	
18	2240, 1670	5.39^{ddd}	2.78^{ddd}	2.27^{ddd}	3.62^{dddd}	4.96^{d}	5.40^{d}	6.37^{d}	300
		9.0	13.8	13.8	8.0	5.2	7.5	7.5	
		6.0	9.0	8.0	5.2				
		0.5	2.2	6.0	2.2				
					0.5				
19	1720, 1700,	5.37^{dd}	2.52^{ddd}	2.03^{ddd}	3.37^{ddd}	5.11^{d}	5.04^{d}	6.16^{d}	3.28^{s}(COOMe) 333
	1620, 1600	9.0	13.0	13.0	8.0	6.1	7.4	7.4	
		6.5	9.0	8.0	6.1				
			2.3	6.5	2.3				
22	1650, 1630,	5.43^{dd}	3.57^{dd}	2.80^{dd}	—	—	6.16^{d}	6.64^{d}	3.59^{s}(COOMe), 9.81$^{br.\,d}$(10-H) 331
	1600, 1520	12.0	15.3	15.3			7.5	7.5	
		6.5	12.0	6.5					
		3-H	2-Ha[b]	2-Hb[c]	1-H	9a-H			
23	2240, 1690	5.17^{ddd}	2.67^{ddd}	2.42^{ddd}	3.58^{ddt}	5.67^{d}			306
		7.8	13.0	13.0	7.0	5.6			
		6.0	7.8	7.0	5.6				
		0.8	5.6	6.0	5.6				
					0.8				
		3-H	2-Ha[b]	2-Hb[c]	1-H	10b-H	6-H	5-H	
25	1720, 1660,	4.97^{dd}	3.22^{dd}	2.01^{dd}	—	5.56^{s}	5.16^{d}	5.95^{d}	0.82^{t}, 1.21^{t}, 3.80^{m}, 4.18^{m}(COOEt) 436
	1630, 1600	8.7	13.0	13.0		—	7.6	7.6	
		6.5	8.7	6.5					
27	2250, 2200,	5.37^{d}	—	4.43^{d}	—	5.57^{s}	5.44^{d}	6.56^{d}	401
	1680, 1630	6.4		6.4		—	8.0	8.0	

a) **18**, **19**, **22**, **27** were measured in CD_3CN and **23**, **25** in $CDCl_3$. b) A hydrogen cis to 3-H. c) A hydrogen trans to 3-H.

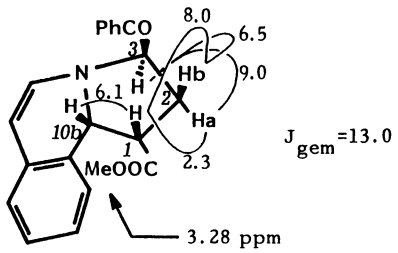


Fig. 3. Stereostructure and ^{1}H-NMR spectral data of **19**.

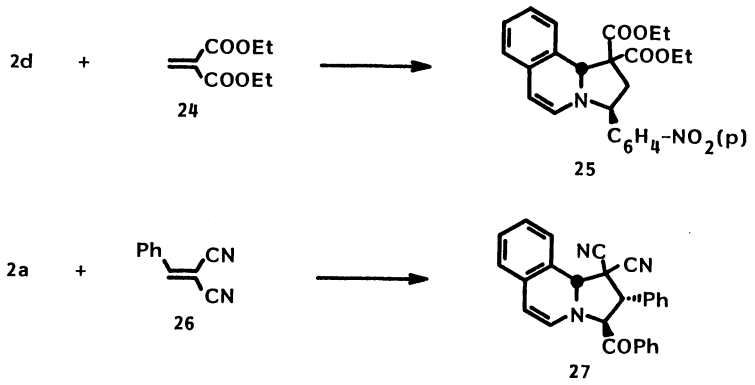
positions and with an undetermined configuration at the 3-position was built up and the coupling constants between 2-Hs and 3-H were estimated. As the result, the structure of **19** was determined as the endo 3+2 cycloadduct to the anti form of **2a**, whose formation was mostly predictable from our rule founded in the preceding paper.[1]

Contrary to the poor stereoselectivity of the cycloaddition between **2d** and **17a** mentioned above, a similar reaction of **2d** with diethyl 2-methylenemalonate **24** which carries two electron-withdrawing substituents at the same carbon was highly selective giving the single 3+2 cycloadduct **25** in a quantitative yield (Scheme 4 and Table 3).

The purification of **25** ended in failure because of its instability, but the ^{1}H-NMR spectrum as well as mass spectrum (Table 4) confirms the tetrahydropyrrolo[2,1-*a*]isoquinoline structure of **25**. The only ambiguousness is the configuration at the point of fusion (10b-H), which was tentatively assigned as shown in Scheme 4 (10b-H is trans to 3-H) on the basis of the mechanistic consideration discussed using Fig. 4 in the following section.

The stereo- and regioselective cycloadduct **27** was similarly obtained in the cycloaddition of **2a** to 2-benzylidenemalononitrile **26**.

The stereochemical features revealed in the cycloadditions to acrylic and related olefins are summarized in Fig. 4. It is quite understandable that the reactions of **2a** and **5** with acrylic olefins **17** have proceeded in a highly regio- and stereoselective fashion through the endo approach **C** (W=COPh, the case of isoquinolinium ylide) of **17** to the anti form of the ylides, because it is now known from our previous work[1] that the ylide **2a** as well as **5**, each of carbonyl-stabilized type, is more stabilized in the anti form than the syn form. On the other hand, the nonstereoselective cycloaddition of **2d** was also predictable. The ylide **2d** carrying a ylide-stabilizing substituent of noncarbonyl type has a similar stability in the anti and syn forms and hence the both endo approaches **C** and **D** (W=*p*-$NO_2C_6H_4$) seem



Scheme 4.

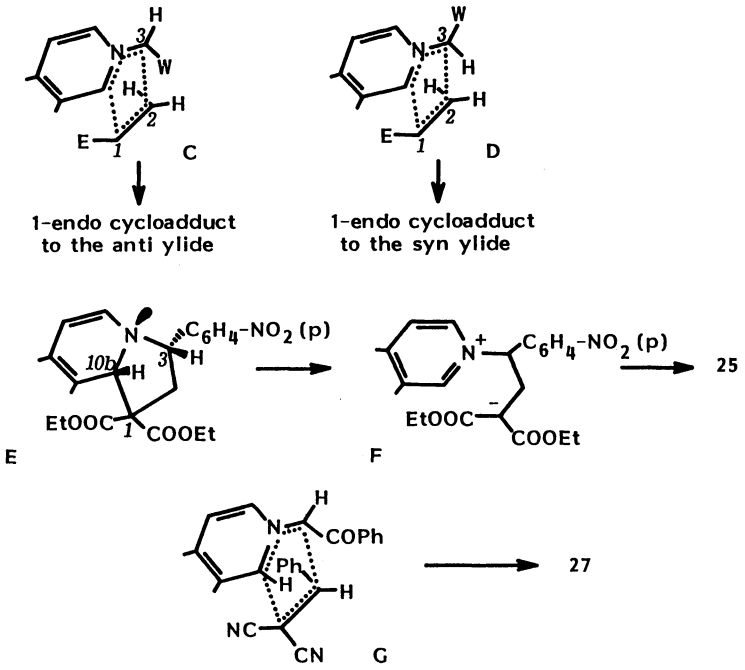


Fig. 4. Stereochemistry in the cycloadditions of **2** to acrylic **17** and related olefins **24, 26.**

likely to compete with the comparable easiness.

Surprising is the formation of single cycloadduct **25** in the reaction of **2d** with the 2-methylenemalonate **24**. We anticipated a kinetically nonstereoselective cycloaddition in this case because all the situation looked about the same to the cycloaddition to **17a**. This can be explained as follows: In this reaction also two isomeric cycloadducts **25** and **E** should have been formed through the energetically almost equal two endo approaches. As the both cycloadducts carry two electron-withdrawing ester groups at the 1-position, the 1—10b bond is readily cleaved into the stable betaine intermediate **F**. The recyclization of **F** must occur in a direction of producing the thermodynamically more stable cycloadduct **25** of the two. Such bond cleavage forming a betaine intermediate has been observed in the hydroalkylidenation reaction using pyridinium methylides[7] and will be discussed later.

In the cycloaddition between **2a** and 2-benzylidenemalononitrile **26** are possible two endo approaches to the anti form of **2a**. However, the reaction has trod the approach **G** leading to **27**. This high selectivity may be the result from either of the attractive interaction between the phenyl plane of **26** and the heteroaromatic plane of **2a** or the steric repulsion between the phenyl group and the benzoyl moiety of the anti form of **2a** as shown in Fig. 4.[8]

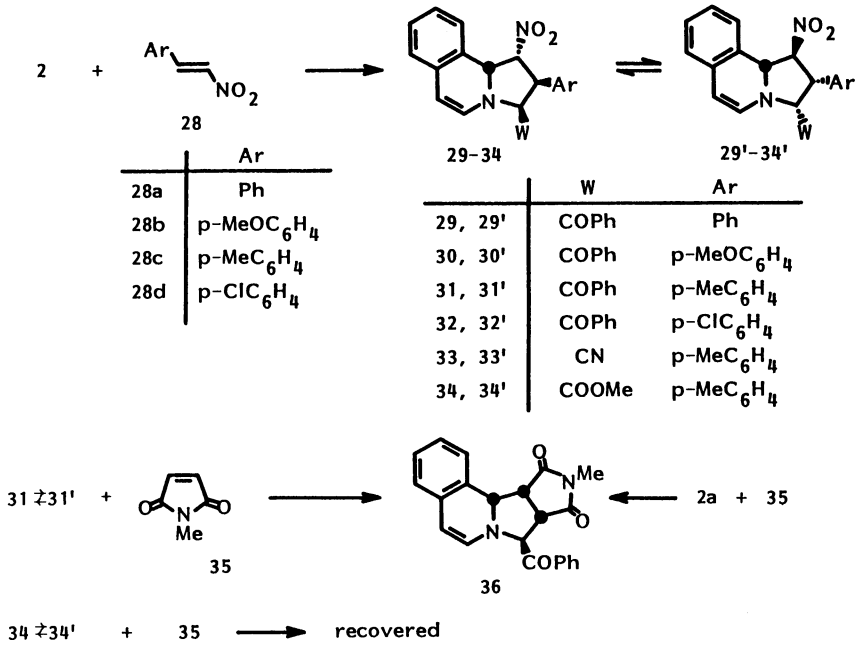
Cycloadditions to Nitro Olefins. The reactions of isoquinolinum ylides **2** with β-nitrostyrenes **28** proceeded at room temperature affording quantitative yields of 1:1 adducts in all cases (Scheme 5). The ^{1}H-NMR measurement of crude products showed that the product was, more or less in each case, composed of two stereoisomers of 3+2 cycloadduct and that the isomer ratio was dependent upon the solvent used for the ^{1}H-NMR measurement and also the time after the ^{1}H-NMR sample was prepared.

Although one isomer of the two or the both could be often separated in an almost pure form through crystallization or precipitation, it was unsuccessful to tell which of the two was the initial cycloadduct (kinetical product) because of the poor solubility and too rapid equilibration of the cycloadducts.

After all, it was concluded that the cycloadducts to **28** were under an equilibrium control (or thermodynamical control) and the energy barrier for the equilibrium was quite small. Their structures were assigned on the basis of the ^{1}H-NMR spectra, the chemical conversions, the molecular model inspection, and the proposed mechanism for the isomerization, all of which will be discussed soon later: **29**—**34**: the 1-endo-2-exo cycloadducts of the anti form of the ylides **2** as kinetically controlled products; **29′**—**34′**: the 1-exo-2-endo cycloadducts of the syn form of **2** as thermodynamically controlled products (Scheme 5).

Table 5 summarizes all the results obtained in the reactions of **2a**—**c** with several β-nitrostyrenes **28a**—**d**. The melting points are given only for the cycloadducts isolated in a pure form through crystallization or precipitation. The structural assignment for the cycloadducts formed from **2a**+**28a** and **2a**+**28d** was impossible because the only solvent in which they are satisfactorily soluble is DMSO, and in this solvent the equilibration between **29** and **29′** (also **32** and **32′**) is finished in a short time.

As shown in Scheme 5, the cycloadducts **31**+**31′** underwent the retro cycloaddition, in DMSO at room temperature, going back to the nitrostyrene **28c** and the ylide **2a** which was quantitatively captured with *N*-methylmaleimide **35** as the maleimide cycloadduct **36**. However, it is not likely that this retro reaction is deeply related with the isomerization between **31** and **31′** since the retro reaction is too slow compared with the isomerization (50 and 100% of **36** were formed after 4 and 48 h, respectively, at room temperature in

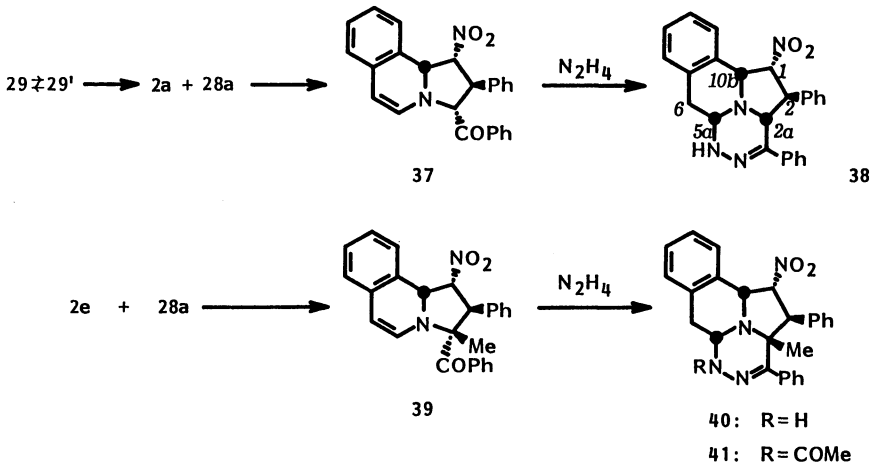


Scheme 5.

Table 5. Cycloadditions to β-nitrostyrenes **28**

Ylide	Olefin	Conditions[a]		Product[b]	Yield/%[c]	Mp(θ_m/°C) and solvent for crystallization[d]		Isomer ratio in DMSO-d_6[e]
		Temperature	Time/h					
2a	**28a**	rt	5 min	**29**⇄**29′**	100	**29** or **29′**	(CHCl$_3$) 129—130	1 : 1
2a	**28b**	rt	5 min	**30**⇄**30′**	100	**30**	(CHCl$_3$) 130—131 (d)	
2a	**28c**	rt	2	**31**⇄**31′**	100	**31**	(Me$_2$CO) 155—157 (d)	1 : 1
						31′	(CHCl$_3$) 146—148 (d)	
2a	**28d**	rt	12	**32**⇄**32′**	100	**32** or **32′**	(CHCl$_3$) 149—150	1 : 1
2b	**28c**	rt	1	**33**⇄**33′**	100	**33**	(CHCl$_3$) 144—146	
2c	**28c**	rt	30 min	**34**⇄**34′**	100	**34′**	(EtOEt) 152—154	1 : 1

a) Carried out in chloroform. b) All yellow solid. c) Isolated yields. d) One isomer was less soluble than the other, being separated in a pure form. e) Very rapid equilibration was observed in DMSO. The ratio was based on the ^{1}H-NMR spectrum.



Scheme 6.

DMSO while the equilibration is completed in less than a few minutes under the same conditions). In fact, in spite of the ready isomerization between **34** and **34'**, the cycloadducts from the ylide **2c** bearing an ester substituent, at room temperature in DMSO, they never undergo the retro reaction with **35** even under harder conditions. As a conclusion, this rapid equilibration takes place *via* a betaine intermediate formed by the 1—10b bond cleavage of the cycloadduct. This will be discussed in detail in the following section.

The rapid equilibration is partly attributable to the high stability of the intermediary betaine compound (**J** in Fig. 6). If the 5—6 double bond of cycloadducts is reduced, such bond cleavage may be suppressed. In order to consume the 5—6 double bond and also to make the conformation of the pyrrolidine ring rigid, the equilibrating mixture of **29** and **29'** was allowed to react with hydrazine hydrate under reflux in ethanol producing a single isomer of the expected diazacyclazine derivative **38** (Scheme 6).

The structure of **38** was determined on the basis of the ^{1}H-NMR spectrum (Fig. 5) and the molecular model inspection: The 2-H is trans both to the 2a-H and 1-H (J_{2-2a}=3.5 and J_{2-1}=6.0 Hz) and the 1-H is cis to the 10b-H (from the molecular model analysis and J_{1-10b}=9.5 Hz). To our surprise, this coupling pattern around the pyrrolidine ring was found completely different from those of **29** (J_{3-2}=8.5, J_{2-1}=4.0, and J_{1-10b} could be about 7 Hz) and **29'** (J_{3-2}=J_{2-1}=J_{1-10b}=8.0 Hz), showing that **38** was derived from an isomeric cycloadduct **37** which was formed by the isomerization of **29** or **29'** under the reaction conditions. The coupling pattern of **31** with a medium-small-medium coupling was once observed in the 1-endo-2-exo cycloadducts of symmetrical trans olefins to the anti form of **2** as the kinetical products.[1]

Now, it is clear that **29** is the 1-endo-2-exo cycloadduct to the anti form of **2** as a kinetically

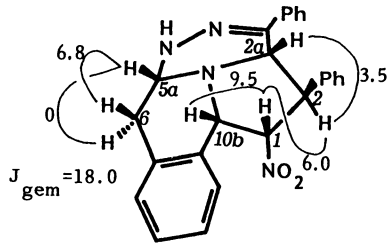


Fig. 5. Stereostructure and ^{1}H-NMR spectral data of **38**.

controlled product, **29'** is the 1-exo-2-endo cycloadduct to the syn form of **2** as a thermodynamically controlled product formed through the isomerization of **29** *via* a betaine intermediate, and that **38** was derived from another thermodynamical cycloadduct **37**, the 1-endo-2-exo 3+2 cycloadduct to the syn form of **2a**. This second thermodynamic cycloadduct **37** may have been formed, under forced conditions, through the retro cycloaddition of **29** (Scheme 6).

The similar reaction of isoquinolinium 1-benzoylethylide **2e** with **28a** and the subsequent cyclization with hydrazine gave **40** also as a single isomer in 21% of total yield. The structural inspection using the ^{1}H-NMR spectra of **40** and its *N*-acetylated derivative **41** confirmed the 1-endo-2-exo skeleton of the nonisolated cycloadduct **39** as shown in Scheme 6.

The IR and ^{1}H-NMR spectra of the cycloadducts **29**—**34** and **29'**—**34'** are listed in Table 6. These spectra are consistent with the proposed structures for each isomers. The both ester methyls at the 3-position of **34** and **34'** are strongly shielded by the fused benzene ring and/or the adjacent phenyl ring.

The stereochemical variety in the cycloadditions of isoquinolinium ylides **2** to nitrostyrenes **28** is summarized in Fig. 6 with an exemplified reaction of **2a** with **28a**. This cycloaddition proceeds through the 1-endo-2-exo approach **H** of **28a** to the anti form of **2a**, just like the cycloadditions of heteroaromatic

Table 6. Spectral data for the cycloadducts to nitro olefins **28**

	IR (cm^{-1})	^{1}H-NMR Spectra (δ, ppm and Hz)						
		Solvent[a]	3-H	2-H	1-H	10b-H	6-H	5-H	Others
29	1670, 1630, 1540	D	6.27^d	4.43^{dd}	5.90^m	5.90^m	5.23^d	6.52^d	
			8.5	4.0	b)			7.0	
29'		D	5.90^m	4.75^t	5.90^m	5.12^d	5.60^d	6.43^d	
			8.0	8.0	8.0			7.2	
30	1670, 1620, 1540, 1510, 1250	A	6.15^d	4.55^{dd}	5.88^{dd}	6.03^d	5.28^d	6.50^d	3.67^s (*p*-MeO)
			8.5	4.4	6.6			7.4	
30'		A	5.84^d	4.73^t	5.88^{dd}	5.20^d	5.63^d	6.43^d	3.63^s (*p*-MeO)
			8.0	8.0	7.3			7.5	
31	1670, 1630, 1540, 1450, 1370, 1220	D	6.22^d	4.48^{dd}	5.84^{dd}	5.92^m	5.22^d	6.53^d	2.12^s (*p*-Me)
			8.5	4.0	7.0			7.5	
31'		A	5.83^d	4.73^t	5.90^{dd}	5.20^d	5.63^d	6.43^d	2.12^s (*p*-Me)
			8.8	8.8	7.9			7.7	
		D	5.23	4.70	5.90	5.12	5.59	6.43	
32	1670, 1630, 1540	D	6.26^d	4.59^{dd}	5.90^m	5.90^m	5.23^d	6.55^d	
			8.5	4.0	b)			7.3	
32'		D	5.90^m	4.79^{dd}	5.90^m	5.12^d	5.63^d	6.45^d	
			8.0	7.5	7.5			7.3	
33	2250, 1630, 1550, 1450, 1370	A	5.61^d	4.47^{dd}	6.02^{dd}	5.83^d	5.40^d	6.43^d	2.33^s (*p*-Me)
			8.2	5.5	7.2			7.8	
33'		CF	4.73^d	4.32^t	5.62^{dd}	5.18^d	5.77^d	6.35^d	2.32^s (*p*-Me)
			8.0	8.0	7.5			7.6	
		A	5.20	4.68	6.00	5.23	5.82	6.52	
34	1740, 1610, 1550, 1360	D	5.05^d	4.34^{dd}	5.92^m	5.92^m	5.13^d	6.34^d	2.27^s (*p*-Me), 3.17^s (COOMe)
			9.0	3.6	b)			7.7	
34'		A	4.63^d	4.68^t	5.98^t	5.22^d	5.62^d	6.38^d	2.29^s (*p*-Me), 3.23^s (COOMe)
			8.0	8.0	8.0			7.5	

a) D: DMSO-d_6; A: acetone-d_6; CF: $CDCl_3$. b) No coupling constant was given.

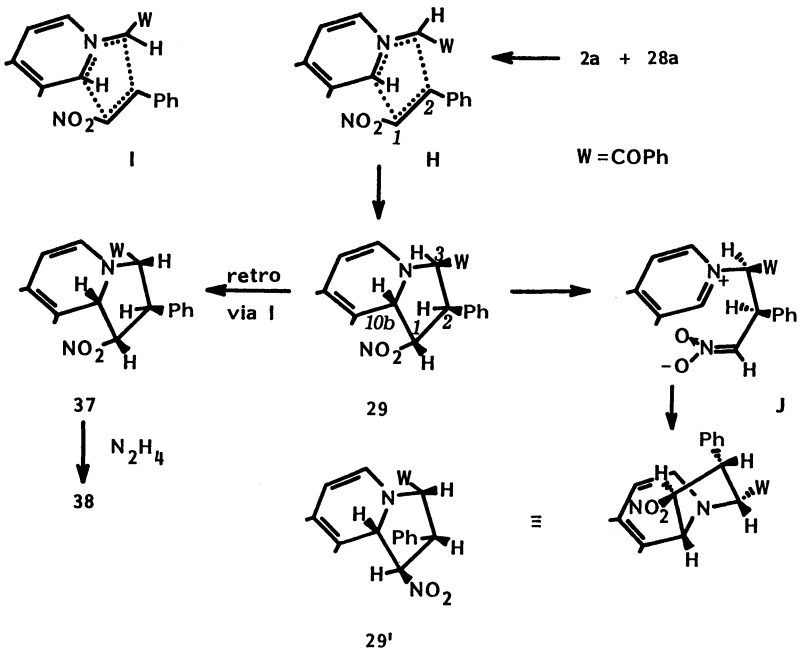


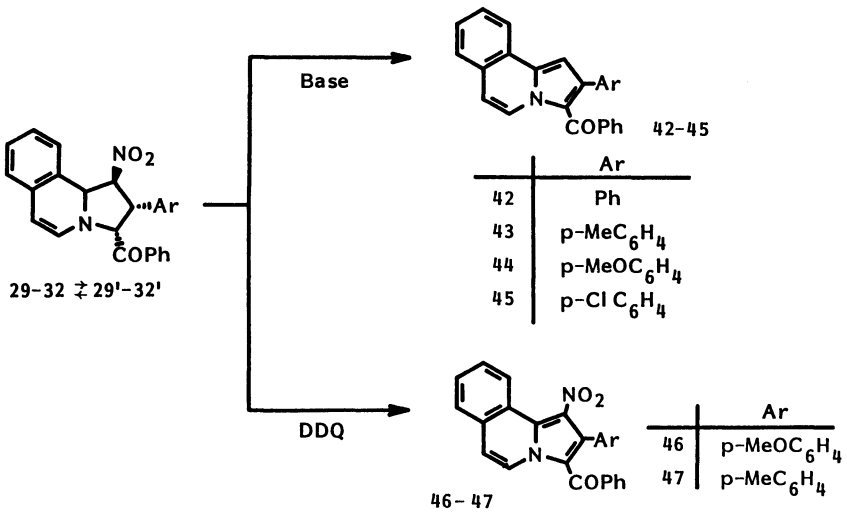
Fig. 6. Stereochemical course of the cycloaddition of **2a** to **28a**.

N-ylides to symmetrical trans olefins,[1] giving **29** as a kinetically controlled cycloadduct. This product **29** undergoes a rapid bond cleavage at the 1—10b bond leading to a betaine intermediate **J**. This easy betaine formation must have been induced by the anion stabilization with the nitro group and also by the cation stabilization in the isoquinolinium ring. The recyclization at the other side of the isoquinoline ring gives **29′** as a thermodynamically controlled cycloadduct. As the thermodynamical stability between **29** and **29′** looks about the same and the energy barrier between **29** and **J** and between **J** and **29′** might be small, they come into a rapid equilibration with the comparable isomer ratio. On the other hand, the kinetical cycloadduct **29** can undergo a slow retro cycloaddition providing **2a** and **28a** which recombine through the 1-endo-2-exo approach **I** to the syn form of **2a** giving the second thermodynamic cycloadduct **37**. Similar isomerization of the kinetical cycloadduct into two isomeric cycloadducts through a betaine intermediate or a retro cycloaddition path will be again discussed in the following section.

When the cycloadducts **29—32** and **29′—32′** were treated with bases, they were found to aromatize into the corresponding pyrrolo[2,1-*a*]isoquinoline derivatives **42—45** with the elimination of the nitro moiety (Scheme 7 and Table 7). Although the yields were not so high, such nitrous acid elimination is important as a method of synthesizing the indolizine derivatives carrying no electron-withdrawing substituent at the 1-position. It was also found that triphenylphosphine was even more effective, but the reaction mechanism is not clear so far.

The aromatization into the indolizines **46—47** carrying a nitro group at the 1-position was achieved by the usual dehydrogenation using DDQ (Scheme 7 and Table 7).

Cycloadditions to Unsymmetrical trans Olefins. Isoquinolinum methylides **2**, which belong to the most reactive heteroaromatic *N*-ylide, were found to react with unsymmetrically substituted trans olefins such as (*E*)-1-(*p*-methylbenzoyl)-2-phenylethene **48a**, cinnamaldehyde **48b**, crotonaldehyde **48c**, and (*E*)-1-benzoylpropene **48d** at room temperature, but rather slowly compared with the cycloadditions to other dipolarophiles previously employed. As the reactions under heating generally lead to the contamination of cycloadduct by some secondary products formed through the isomerization, dehydrogenation, or decomposition of the initially formed cycloadduct



Scheme 7.

Table 7. Conversion of the cycloadducts of β-nitrostyrenes into benzo[*g*]indolizines

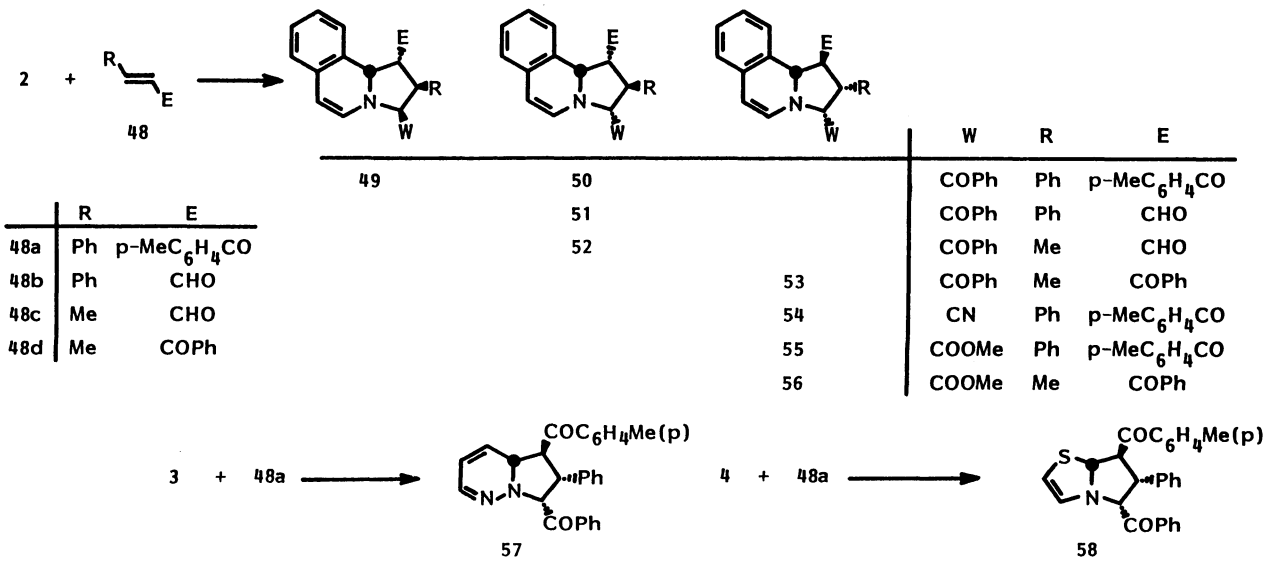
Cycloadduct	Base or oxidant	Reaction conditions		Time/h	Product[b]	Mp θ_m/°C	Yield/%[c]
		Solvent[a]	Temperature				
29⇄29′	PPh_3	AN	reflux	24	**42**	219—222	28
30⇄30′	NEt_3	CF	rt	21	**43**	191—193	58
31⇄31′	DBU	BZ	rt	22	**44**	203—205	28
	PPh_3	BZ	reflux	8			46
32⇄32′	PPh_3	AN	reflux	44	**45**	178—180	37
30⇄30′	DDQ	BZ	reflux	24	**46**	198—201	76
31⇄31′	DDQ	BZ	reflux	12	**47**	227—230	72

a) AN: acetonitrile; CF: chloroform; BZ: benzene. b) All yellow prisms. c) Isolated yields.

and since such cycloadducts are usually not so stable enough to be separated or purified safely, only limited numbers of dipolarophiles were used. No clear result was given in the reactions with such unreactive olefins as crotonates, cinnamates, (*E*)-4-phenyl-3-propen-2-one, and (*E*)-3-penten-2-one which required harder reaction conditions and therefore resulted in the complex mixture of products. The results are summarized in Scheme 8 and Table 8.

Three different types of 3+2 cycloadducts were isolated in the reactions with **48**, depending upon the nature of substituents of the ylide **2** and olefin **48** and also upon the reaction conditions. The reaction of **2a** with **48a** in acetonitrile precipitated a labile cycloadduct **49** in a pure form. This cycloadduct **49** was found to readily isomerize into **50** in DMSO even at room temperature. When the same reaction was carried out in chloroform, no precipitate appeared and only **50** was obtained in a quantitative yield. These facts indicate that **49** and **50** are the kinetic and thermodynamic cycloadducts, respectively. The third type of cycloadducts are **53**—**58** which were formed from either the alkyl-substituted vinyl ketone **48d**, the ylides **2b** and **2c** carrying a cyano or ester ylide-stabilizing substituent, or the other types of ylides **3** and **4**.

Each type of these cycloadducts showed a characteristic coupling pattern among the methine hydrogens on the newly formed five-membered ring as shown in Table 9. The product **49** showed similar couplings to the kinetically controlled cycloadduct between **2** and symmetrical trans olefins,[1] being assigned to be the 1-endo-2-exo cycloadduct to the anti form of **2a** as a kinetical product. Its isomer **50** exhibited a coupling pattern similar to both **38** (hence **37**) and the thermodynamically controlled cycloadduct of **2** to symmetrical trans olefins (1-exo-2-endo cycloadduct to the anti ylide). Based on this fact and also its chemical conversion into a diazacyclazine derivative which will be described



Scheme 8.

TABLE 8. CYCLOADDITIONS TO UNSYMMETRICAL TRANS OLEFINS **48**

Ylide	Olefin	Reaction conditions			Product (yield/%)[b]				
		Solvent[a]	Temperature	Time/h					
2a	**48a**	AN	rt	4	**49** (46)	**50** (54)			
		CF	rt	1.5		**50** (100)			
2a	**48b**	DM	rt	30 min		**51** (100)			
2a	**48c**	CF	rt	30 min		**52** (80)			c)
2a	**48d**	CF	rt	30 min			**53** (86)		c)
2b	**48a**	CF	rt	1			**54** (100)		
2c	**48a**	CF	rt	3			**55** (100)		
2c	**48d**	CF	rt	20 min			**56** (70)		c)
3	**48a**	CF	rt	14			**57** (100)		
4	**48a**	CF	rt	14			**58** (100)		

a) AN: acetonitrile; CF: chloroform; DM: dichloromethane. b) All isolated yields. c) An additional cycloadduct was formed but its stereostructure could not be determined.

Table 9. Spectral data for the cycloadducts to unsymmetrical trans olefins **48**

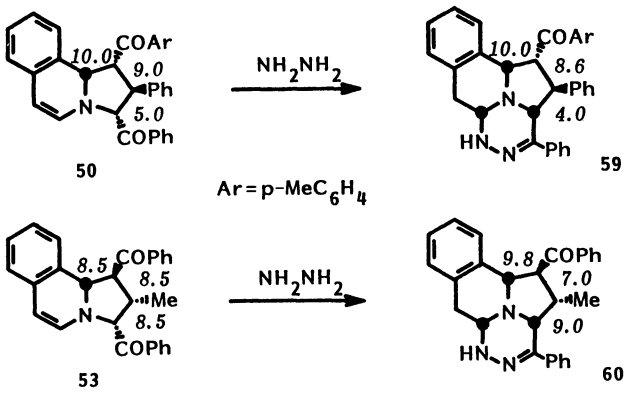
	IR (cm^{-1})	^{1}H-NMR Spectra measured in deuteriochloroform (δ, ppm, and Hz)										M$^+$ (m/z)
		3-H	2-H	1-H	10b-H	6-H	5-H	J_{3-2}	J_{2-1}	J_{1-10b}		
49	1680, 1660, 1635, 1605	6.00^d	4.16^{dd}	4.96^{dd}	5.16^d	5.16^d	5.83^d 7.4	8.0	5.5	7.6	2.33^s (p-Me)	496
50	1690, 1670, 1600	5.07^d	3.83^{dd}	4.62^{dd}	5.28^d	5.52^d	6.30^d 7.5	5.0	9.0	10.0	2.23^s (p-Me)	496
51	1660, 1620, 1595	5.02^d	3.93^{dd}	3.68^{ddd}	5.06^d	5.47^d	6.20^d 7.3	4.3	8.0	9.1	9.70^d (CHO)	379
52[a]	1720, 1690	4.69^d	2.68^{ddq}	3.06^{ddd}	5.07^d	5.40^d	6.16^d 7.5	4.5	7.6	8.9	1.28^d (2-Me), 9.73^d (CHO)	317
53[b]	1690, 1680, 1610, 1600	5.22^d	3.02^{ddq}	4.36^t	5.24^d	5.48^d	6.21^d 7.3	8.5	8.5	8.5	0.88^d (2-Me)	393
54	2220, 1678, 1605	4.60^d	3.87^t	4.71^{dd}	5.13^d	5.69^d	6.43^d 7.9	8.1	8.1	8.9	2.33^s (p-Me)	390
55	1740, 1660, 1620, 1600	4.40^d	3.87^{dd}	4.72^{dd}	5.20^d	5.60^d	6.39^d 7.4	9.0	8.1	8.7	2.33^s (p-Me), 3.20^s (COOMe)	423
56[c]	1740, 1670, 1620	4.23^d	2.92^{ddq}	4.40^{dd}	5.25^d	5.42^d	6.20^d 7.5	8.5	10.0	9.0	0.98^d (2-Me), 3.67^s (COOMe)	347
		7-H	6-H	5-H	4a-, 4-, 3-H		2-H	J_{7-6}	J_{6-5}	J_{5-4a}		
57	1690—1660, 1580	5.93^d	4.50^{dd}	4.93^t	5.10—5.94^m		6.72^m	7.9	9.0	9.0	2.37^s (p-Me)	d)
		5-H	6-H	7-H	7a-H	2-H	3-H	J_{5-6}	J_{6-7}	J_{7-7a}		
58	1680, 1670 1600	5.29^d	4.56^{dd}	4.93^{dd}	6.52^d	5.47^d	5.87^d 4.5	7.5	8.2	7.8	2.37^s (p-Me)	425

a) Contaminated by 20% of an isomer which shows 0.92^d (2-Me). b) Contaminated by 14% of an isomer which shows 1.03^d (2-Me). c) Contaminated by 30% of an isomer which shows 1.37^d (2-Me) and 3.77^s (COOMe). d) No parent ion peak was observed.

later, **50** was determined to be the 1-endo-2-exo cycloadduct to the syn form of **2a** as a thermodynamically controlled product, and the same to the others **51—52**.

The coupling pattern of the third type of cycloadducts **53—58** is close to the 1-exo-2-endo cycloadducts **29′—34′** of nitro olefins to the syn form of **2** (see Scheme 5 and Table 6). Thus, they were assigned to be the 1-exo-2-endo cycloadducts to the syn form of **2** as the cycloadducts isomerized through betaine intermediates.

To confirm the structures of the above cycloadducts, rather stable two cycloadducts **50** and **53** were subjected to the cyclization using hydrazine hydrate. As shown in Scheme 9, two types of diazacyclazine derivatives **59** and **60** were obtained. It is clear that the stereochemistry has not changed, in both cases, before and after the cyclization, because the starting materials **50** and **53** showed very similar couplings to those of the products **59** and **60**, respectively. Not only the coupling pattern but also the mode of cyclization supports the proposed



Scheme 9.

structures of **50** and **53**, and hence of **50—52** and **53—58**. Molecular model inspection shows that such hydrazine cyclization is possible only when the 3-benzoyl moiety is endo, and both **50** and **53** were assigned as the cycloadducts of syn ylide.

The stereochemical features observed in the cycloadditions of the ylides **2—4** with unsymmetrically substituted trans olefins **48** are symmarized in Fig. 7 with the cycloaddition example using **2**. In this case also, the kinetically favored approach is the 1-endo-2-exo approach **K** to the anti form of **2** forming the kinetical product **N**. The cycloadduct **49** is an example belonging to this kind. When W is strongly ylide-stabilizing and also the both olefin substituents R and COR′ are highly activating the olefin, the kinetical cycloadduct **N** suffers from a ready retro cycloaddition giving back to the ylide **2** and olefin **48**. They again undego a cycloaddition, but through a different approach **L**, the 1-endo-2-exo approach to the syn form of **2**, producing the thermodynamic cycloadduct **O**. The cycloadducts **50—52** are the examples. When the retro cycloaddition path is forbidden (W is cyano or ester, or the olefin substituents are not highly activating), the kinetical cycloadduct **N** takes another isomerization pathway. As have been observed for the nitrostyrene cycloadducts, the isomerization through a betaine intermediate **M** occurs leading to the 1-exo-2-endo cycloadduct **P** to the syn form of **2**. The cycloadducts **53—56** are the cases.

Experimental

Materials. *N*-Phenacyl-3,5-dimethylpyridinium bromide (mp 200—203 °C, Found: C, 58.56; H, 5.33; N, 4.54%. Calcd for $C_{15}H_{16}ONBr$: C, 58.82; H, 5.23; N, 4.58%) and *N*-cyanomethyl-3,5-dimethylpyridinium bromide (mp 143—145 °C, Found: C, 47.36; H, 4.84; N, 12.15%. Calcd for $C_9H_{11}N_2Br$: C, 47.58; H, 4.85; N, 12.33%) were prepared by

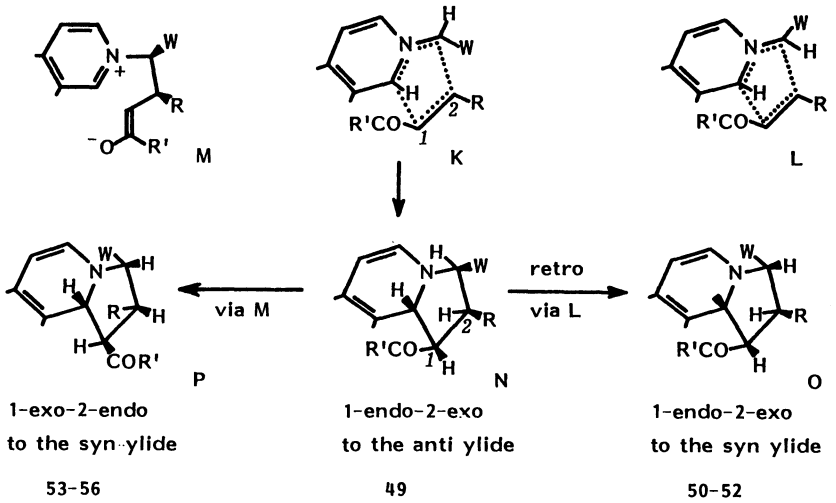


Fig. 7. Stereochemical course of the cycloaddition between **2** and **48**.

the reactions of 3,5-dimethylpyridine with α-bromoacetophenone and α-bromoacetonitrile, respectively. *N*-(*p*-Tolyl)citraconimide **6** was obtained by the reaction between citraconic anhydride and *p*-methylaniline followed by the treatment with acetic anhydride in the presence of sodium acetate.[9] Diethyl methylenemalonate **24** and benzylidenemalononitrile **26** were synthesized by the condensation of diethyl malonate with paraformaldehyde[10] and of malononitrile with benzaldehyde,[11] respectively. β-Nitrostyrenes **28a—d** were all prepared from the condensations between nitromethane and *p*-substituted benzaldehydes:[12] **28a**: Pale yellow prisms ($CHCl_3$), mp 58 °C; **28b**: Yellow prisms (EtOH), mp 81—82 °C; **28c**: Yellow needles ($CHCl_3$), mp 92—94 °C; **28d**: Pale yellow prisms ($CHCl_3$). (*E*)-1-(*p*-Methylbenzoyl)-2-phenylethene **48a** and (*E*)-1-benzoylpropene **48d** were obtained by the condensations between *p*-methylacetophenone and benzaldehyde[13] and between triphenylphosphonium phenacylide and acetaldehyde,[14] respectively. Other olefinic dipolarophiles **15—17**, **35**, and **48b—c** were all commercially available.

General Procedure for the Cycloadditions of 1a—e and 2a to Methyl-substituted Olefins 6 and 15. To the equivalent suspension of a ylide precursor and an olefin in dry chloroform (30 ml for the 1 mmol-scaled reaction), was slowly added an equivalent amount of triethylamine at room temperature. The mixture was allowed to stir at room temperature (one exception: The reaction between **2a** with **15** was carried out under reflux in chloroform) until all the precursor salts dissolved into a clear solution. After the completion of cycloaddition, the mixture was poured into ice water and extracted with chloroform twice (20 ml×2). The combined extracts were dried over $MgSO_4$ and evaporated *in vacuo* below room temperature. The crude oily material was weighed and subjected to the ^{1}H-NMR measurement. Often it solidified when triturated with petr. ether and/or ether. The reaction conditions, the melting points and yields of products are listed in Table 1. In every case the purification of cycloadduct was unsuccessful because of their lability. Therefore, the solidified products, or oily product itself, were submitted for the spectral measurement. Table 2 shows all the spectral data of cycloadducts **7—14** and **16**.

General Procedure for the Cycloadditions of 2 and 5 to Acrylic 17 and Related Olefins 24 and 26. The cycloadditions were performed by the similar procedures described above under the reaction conditions listed in Table 3. The melting points and yields of products are shown in Table 3 and the spectral data in Table 4. Other data are given as follows: **18**: Yellow prisms ($CHCl_3$–ether); ^{1}H-NMR ($CDCl_3$) δ=2.20—2.70 (2H, m, 2-H), 3.30—3.60 (1H, m, 1-H), 4.96 (1H, d, J_{10b-1}=5.2 Hz, 10b-H), 5.23 (1H, dd, J_{3-2}=9.0 and 6.0 Hz, 3-H), 5.37 (1H, d, J_{6-5}=7.5 Hz, 6-H), 6.16 (1H, d, J_{5-6}=7.5 Hz, 5-H), 6.90—7.70, and 7.80—8.10 ppm (9H, each m, ArH); Found: C, 80.06; H, 5.16; N, 9.04%. Calcd for $C_{20}H_{16}ON_2$: C, 79.98; H, 5.37; N, 9.33%. **19**: Yellow prisms (ether); Found: C, 75.42; H, 5.73; N, 4.28%. Calcd for $C_{21}H_{19}O_3N$: C, 75.65; H, 5.74; N, 4.20%. **20+21**: ^{13}C-NMR ($CDCl_3$) the major: δ=37.40 (t, 2-C), 38.57 (d, 1-C), 63.28, and 64.65 (each d, 3- and 10b-C); the minor: δ=35.20 (t, 2-C), 36.33 (d, 1-C), 63.57, and 65.92 ppm (each d, 3- and 10b-C). The intensity ratio was 2/1. **23**: colorless needles (EtOH); ^{13}C-NMR ($CDCl_3$) δ=33.3 (t, 2-C), 36.7 (d, 1-C), 68.0, 72.4 (each d, 3- and 9a-C), and 196.9 ppm (s, PhCO); Found: C, 70.44; H, 4.45; N, 9.07%. Calcd for $C_{18}H_{14}ON_2S$: C, 70.56; H, 4.61; N, 9.14%.

General Procedure for the Cycloadditions of 2 to Nitro Olefins 28. These cycloadditions were carried out using each equivalent amount of **2** and **28** according to the procedure mentioned above under the reaction conditions shown in Table 5. The results and the spectral data of cycloadducts are summarized in Table 5 and 6, respectively. The methods for separation of the isomeric cycloadducts and other data are given as follows:

29+29′: Either of **29** or **29′** was precipitated when the reaction mixture was condensed *in vacuo*. **29** or **29′**: Yellow needles ($CHCl_3$); MS *m/z* (rel intensity, %) 347 (M^+−49, 4), 105 (76), and 77 (base peak); Found: C, 75.85; H, 5.11; N, 7.16%. Calcd for $C_{25}H_{20}O_3N_2$: C, 75.74; H, 5.09; N, 7.07%.

30+30′: **30** was separated as precipitate during the cycloaddition in $CHCl_3$ and the evaporation of the filtrate gave a mixture of **30** and **30′**. **30**: Yellow needles ($CHCl_3$); MS *m/z* (rel intensity, %) 377 (M^+−49, 10), 348 (6), 228 (42), 105 (66), and 77 (base peak); Found: C, 72.75; H, 5.16; N, 6.79%. Calcd for $C_{26}H_{22}O_4N_2$: C, 73.22; H, 5.20; N, 6.57%. **30+30′**: Yellow solid; Found: C, 73.27; H, 5.10; N, 6.49%. Calcd for $C_{26}H_{22}O_4N_2$: C, 73.22; H, 5.10; N, 6.49%.

31+31′: **31′** was precipitated when the reaction mixture was condensed *in vacuo* at room temperature, and **31** was obtained as precipitate from the solution of **31′** in acetone. **31**: Yellow prisms (Me_2CO). **31′**: Yellow needles ($CHCl_3$); MS *m/z* (rel intensity, %) 377 (M^+−23, 17) and 361 (base peak); Found: C, 75.36; H, 5.28; N, 6.85%. Calcd for $C_{26}H_{22}O_3N_2$: C, 76.08; H, 5.40; N, 6.83%.

32+32′: Either of **32** or **32′** was isolated when the reaction mixture was evaporated *in vacuo* and the residue was triturated with ether. **32** or **32′**: Yellow needles ($CHCl_3$); MS *m/z* (rel intensity, %) 431 (M^+, 1) and 278 (base peak); Found: C, 69.78; H, 4.37; N, 6.18%. Calcd for $C_{25}H_{19}O_3N_2Cl$: C, 69.52, H, 4.40; N, 6.49%.

33+33′: **33′** was obtained as yellow viscous oil when the reaction solvent was removed *in vacuo*, and the solution of **33′** in $CHCl_3$ precipitated **33** after a long period of time at room temperature. **33**: Yellow needles ($CHCl_3$); MS *m/z* 315 (M^+−16), 290, and 282 (M^+−49, base peak); Found: C, 72.61; H, 5.22; N, 12.41%. Calcd for $C_{20}H_{17}O_2N_3$: C, 72.49; H, 5.17; N, 12.68%.

34+34′: **34′** was obtained when the oily crude product was treated with ether and isomerized in $CHCl_3$ at room temperature into a mixture of **34** and **34′**. **34′**: Yellow prisms (ether); MS *m/z* (rel intensity, %) 364 (M^+, 26), 317 (M^+−47, 72), and 258 (base peak); Found: C, 68.91; H, 5.63; N, 7.90%. Calcd for $C_{21}H_{20}O_4N_2$: C, 69.21; H, 5.53; N, 7.60%.

Retro Cycloadditions of 31+31′ and 34+34′ in the Presence of N-Methylmaleimide 35. A mixture of **31** and **31′** (1:1) in DMSO-d_6 was placed in an NMR sample tube and an equivalent amount of **35** was added. The resulting mixture was observed by ^{1}H-NMR spectroscopy. After 4 h at room temperature, each 50% of **31+31′** and **35** was consumed and the endo cycloadduct **36** was formed. And after 48 h at the same temperature, none of **31**, **31′**, and **35** was in the solution and the only compounds contained were **36** and **28c**. The similar procedure using a mixture of **34**, **34′**, and **35** in DMSO-d_6 showed no formation of the

cycloadduct between **28c** and **35**.

*Reaction of **29**+**29′** with Hydrazine Hydrate Leading to **38**.* To a mixture of **29** and **29′** (396 mg, 1 mmol) in EtOH (20 ml), was added hydrazine hydrate (4 ml) and the resulting mixture was heated under reflux for 6 h. The residue, obtained by evaporation of the solvent *in vacuo*, was treated with ice water (20 ml) and then extracted with ether (20 ml×2). The ether was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was chromatographed over silica gel (C-300) with chloroform giving 127 mg of **38** (31%): Colorless prisms (ether–petr. ether); mp 188 °C; IR (KBr) 3350, 1540, and 1360 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ=2.65 (1H, d, J_{gem}=18.0 Hz, 6-*endo*-H), 3.25 (1H, dd, J_{gem}=18.0 and J_{6-5a}=6.8 Hz, 6-*exo*-H), 3.53 (1H, dd, J_{2-1}=6.0 and J_{2-2a}=3.5 Hz, 2-H), 4.68 (1H, d, J_{5a-6}=6.8 Hz, 5a-H), 4.79 (1H, br.d, J_{2a-2}=3.5 Hz, 2a-H), 4.98 (1H, d, J_{10b-1}=9.5 Hz, 10b-H), 5.03 (1H, dd, J_{1-10b}=9.5 and J_{1-2}=6.0 Hz, 1-H), 5.96 (1H, br.s, NH, D_2O exchangable), and 6.90—7.50 ppm (14H, m, ArH); ^{13}C-NMR ($CDCl_3$) δ=31.77 (t, 6-C), 55.21, 58.67, 63.74, 64.42 (each d, 2-, 2a-, 5a-, and 10b-C), 95.27 (d, 1-C), 123.29, 125.67, 126.31, 127.53, 128.01, 128.31, 128.45, 128.89, 129.18, 131.91 (s), 134.20 (s), 135.76 (s), 141.12 (s), and 145.46 ppm (s, 3-C); MS *m/z* (rel intensity, %) 410 (M^+, 12), 364 (70), and 244 (base peak).

Found: C, 73.29; H, 5.36; N, 13.39%. Calcd for $C_{25}H_{22}O_2N_4$: C, 73.15; H, 5.40; N, 13.65%.

*Cycloaddition between **2e** and **28a** Followed by Hydrazine Cyclization Leading to **40**.* A mixture of *N*-(1-benzoylethyl)isoquinolinium bromide (684 mg, 2 mmol) and **28a** (298 mg, 2 mmol) in dry chloroform (30 ml) was refluxed for 30 min in the presence of NEt_3 (0.28 ml, 2 mmol). The solvent was evaporated *in vacuo*, the residue treated with water (30 ml), extracted with ether (20 ml×2), the ether dried over $MgSO_4$, and then evaporated *in vacuo*. The residue was dissolved in EtOH (30 ml). After hydrazine hydrate (4 ml) was added, the mixture was heated under reflux for 22 h. The ethanol was evaporated *in vacuo*, the residue treated with water (10 ml), extracted with ether (20 ml×2), the ether dried over $MgSO_4$, and evaporated *in vacuo*. The residue was chromatographed over silica gel using chloroform as an eluent to give **40** (264 mg, 31%): Colorless solid; mp 109 °C; IR (KBr) 1550 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ=1.34 (3H, s, Me), 2.73 (1H, d, J_{gem}=18.0 Hz, 6-*endo*-H), 3.30 (1H, dd, J_{gem}=18.0 and J_{6-5a}=6.0 Hz, 6-*exo*-H), 3.92 (1H, d, J_{2-1}=6.8 Hz, 2-H), 4.78 (1H, d, J_{10b-1}=9.5 Hz, 10b-H), 4.90 (1H, d, J_{5a-6}=6.0 Hz, 5a-H), 5.27 (1H, dd, J_{1-10b}=9.5 and J_{1-2}=6.8 Hz, 1-H), 6.04 (1H, br.s, NH, D_2O exchangable), and 6.80—7.28 ppm (14H, m, ArH); MS *m/z* (rel intensity, %) 424 (M^+, 2), 275 (60), and 258 (base peak).

This product **40** was acetylated with acetic anhydride in the presence of a catalytic amount of pyridine at room temperature for 2 d to afford 43% of **41**: Colorless prisms (ether–hexane); mp 161 °C; IR (KBr) 1690 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ=1.33 (3H, s, Me), 2.37 (3H, s, COMe), 3.70 (1H, dd, J_{gem}=18.5 and J_{6-5a}=6.0 Hz, 6-*exo*-H), 3.90 (1H, dd, J_{gem}=18.5 and J_{6-5a}=3.7 Hz, 6-*endo*-H), 4.23 (1H, d, J_{2-1}=4.5 Hz, 2-H), 4.58 (1H, d, J_{10b-1}=8.0 Hz, 10b-H), 5.24 (1H, dd, J_{1-10b}=8.0 and J_{1-2}=4.5 Hz, 1-H), 5.47 (1H, dd, J_{5a-6}=6.0 and 3.7 Hz, 5a-H), and 6.90—7.70 ppm (14H, m, ArH); MS *m/z* (rel intensity, %) 466 (M^+, 1) and 258 (base peak).

Found: C, 72.27; H, 5.77; N, 12.14%. Calcd for $C_{28}H_{26}O_3N$: C, 72.08; H, 5.62; N, 12.01%.

*General Procedure for the Aromatization of **29—32** and **29′—32′** Leading to **42—47**.* To the solution of **29—32** and **29′—32′** (1 mmol in 10 ml of solvent), was added an equivalent amount of PPh_3, NEt_3, DBU, or DDQ. The resulting mixture was allowed to react until all the cycloadduct was consumed (checked on TLC). The base, oxidant, solvent, temperature, and time are listed in Table 7. After the reaction was completed, the solvent was evaporated *in vacuo*. The residue was chromatographed over silica gel using benzene as an eluent to give the aromatized cycloadduct. The melting points and yields of products are summarized in Table 7. Other date are given as follows:

42: Yellow prisms (ether); IR (KBr) 1600 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ=6.82—7.78 (14H, m, ArH), 8.00—8.23 (1H, m, ArH), and 9.23 ppm (1H, d, J=8.0 Hz, 10-H); MS *m/z* (rel intensity, %) 347 (M^+, 8) and 380 (base peak).

Found: C, 86.24; H, 4.97; N, 4.35%. Calcd for $C_{25}H_{17}ON$: C, 86.43; H, 4.93; N, 4.03%.

43: Yellow prisms (ether); IR (KBr) 1610 and 1590 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ=2.20 (3H, s, *p*-Me), 6.70—7.20 (8H, m, ArH), 7.30—7.80 (5H, m, ArH), 8.00—8.20 (1H, m, ArH), and 9.25 ppm (1H, d, J=7.5 Hz, 10-H); MS *m/z* 361 (M^+).

Found: C, 85.87; H, 5.23; N 3.89%. Calcd for $C_{26}H_{19}ON$: C, 86.40; H, 5.30; N, 3.88%.

44: Yellow prisms (benzene–hexane); IR (KBr) 1600, 1520, and 1360 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ=3.64 (3H, s, OMe), 6.54 (2H, br.d, J=9.0 Hz, ArH), 6.80—7.15, 7.50—7.70 (12H, each m, ArH), 8.10 (1H, m, ArH), and 9.23 ppm (1H, d, J=8.0 Hz, 10-H); MS *m/z* (rel intensity, %) 377 (M^+, base peak), 348 (12), 300 (17), 188 (10), 105 (3), and 77 (7).

Found: C, 82.74; H, 5.07; N, 3.71%. Calcd for $C_{26}H_{19}O_2N$: C, 82.83; H, 5.04; N, 3.81%.

45: Orange prisms (ether); IR (KBr) 1610, 1590, 1450, and 1400 cm^{-1}; MS *m/z* (rel intensity, %) 383, 381 (M^+, 13, 40), 241 (94), and 78 (base peak).

Found: C, 78.34; H, 4.27; N, 3.83%. Calcd for $C_{25}H_{16}ONCl$: C, 78.64; H, 4.19; N, 3.67%.

46: Yellow prisms (ether); IR (KBr) 1730, 1620, and 1510 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ=3.66 (3H, s, OMe), 6.57 (2H, br.d, J=9.0 Hz, ArH), 6.90—7.30, 7.30—7.80 (11H, each m, ArH), 8.25—8.50 (1H, m, ArH), and 8.96 ppm (1H, d, J=7.8 Hz, 10-H); MS *m/z* (rel intensity, %) 422 (M^+, 24), 105 (68), and 77 (base peak).

47: Yellow prisms (ether); IR (KBr) 1600, 1570, and 1520 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ=2.31 (3H, s, *p*-Me), 6.87—7.89 (13H, m, ArH), 8.37—8.62 (1H, m, ArH), and 9.06 ppm (1H, d, J=8.0 Hz, 10-H); MS *m/z* (rel intensity, %) 406 (M^+, 56).

Found: C, 77.11; H, 4.63; N, 6.73%. Calcd for $C_{26}H_{18}O_3N_2$: C, 76.83; H, 4.46; N, 6.87%.

*General Procedure for the Cycloadditions of **2—4** to Unsymmetrical trans Olefins **48**.* To the mixture of 1 mmol each of the ylide precursor and **48** in 30 ml of solvent, was added an equivalent amount of NEt_3. The resulting mixture was stirred at room temperature until all the suspension dissapeared. The reaction solvent and time are listed in Table 8. After the completion of cycloaddition, the mixture was poured into ice water and extracted twice (each 20 ml) with dichloromethane. The combined extracts were dried over $MgSO_4$ and evaporated

in vacuo giving crude cycloadduct. As the cycloadducts **49**—**58** are all too labile to be purified through a chromatography or from crystallization, they were subjected to the spectral measurement. The yields and spectral data of cycloadducts are shown in Table 8 and 9, respectively. Other data are given as follows:

49: Yellow needles (CH_3CN); mp 165—167 °C; **50**: Yellow solid; mp 94—96 °C; Found: C, 84.26; H, 5.83; N, 2.84%. Calcd for $C_{33}H_{27}O_2N$: C, 84.40; H, 5.80; N, 2.98%. **51**: Yellow needles (ether); mp 182—185 °C (dec). **52**: Yellow solid; mp 102—104 °C. **53**: Orange solid; mp 61—65 °C. **54**: Orange solid; mp 105—107 °C. **55**: Yellow solid; mp 79—82 °C. **56**: Orange solid; mp 64—70 °C.

*Hydrazine Cyclization of **50** Leading to **59**.* A mixture of **50** (928 mg, 2 mmol) and hydrazine hydrate (4 ml) in EtOH (50 ml) was refluxed for 14 h and the solvent was evaporated *in vacuo*. The residue was treated with ice water, extracted with ether (20 ml×2), the ether dried over $MgSO_4$, and evaporated *in vacuo*. The residue was chromatographed over silica gel (Merck C-200) with ethyl acetate–hexane (1:4) to give **59** (347 mg, 36%): Colorless prisms (Me_2CO); mp 132—133 °C; IR (KBr) 3350, 1700, 1660, and 1600 cm^{-1}; ^1H-NMR ($CDCl_3$) δ=2.28 (3H, s, *p*-Me), 2.77 (1H, br.d, J_{gem}=18.0 Hz, 6-*endo*-H), 3.11 (1H, dd, J_{2-1}=8.6 and J_{2-2a}=4.0 Hz, 2-H), 3.43 (1H, br.dd, J_{gem}=18.0 and J_{6-5a}=6.7 Hz, 6-*exo*-H), 4.09 (1H, dd, J_{1-10a}=10.0 and J_{1-2}=8.6 Hz, 1-H), 4.87 (1H, br.d, J_{5a-6}=6.7 Hz, 5a-H), 4.88 (1H, d, J_{2a-2}=4.0 Hz, 2a-H), 5.04 (1H, d, J_{10b-1}=10.0 Hz, 10b-H), 5.76 (1H, br.s, NH, D_2O exchangable), 6.56 (1H, br.d, J=8.0 Hz, ArH), and 6.64—7.46 ppm (17H, m, ArH); MS *m/z* (rel intensity, %) 483 (M^+, 7), 482 (9), and 244 (base peak).

Found: C, 79.50; H, 6.55; N, 7.92%. Calcd for $C_{33}H_{29}ON_3$: C, 79.82; H, 6.51; N, 7.76%.

*Hydrazine Cyclization of **53** Leading to **60**.* A mixture of **53** (786 mg, 2 mmol) and hydrazine hydrate (4 ml) in EtOH (50 ml) was refluxed for 14 h and the solvent was evaporated *in vacuo*. The residue was treated with ice water, extracted with ether (20 ml×2), the ether dried over $MgSO_4$, and evaporated *in vacuo*. The residue was chromatographed over silica gel with hexane–ethyl acetate (3:1) to give **60** (222 mg, 27%): Colorless needles (EtOH); mp 250—253 °C; IR (KBr) 3200 and 1660 cm^{-1}; ^1H-NMR ($CDCl_3$) δ=1.02 (3H, d, J=7.1 Hz, 2-Me), 2.60—3.08 (3H, m, 6-CH_2 and 2-H), 3.90 (1H, dd, J_{1-10b}=9.8 and J_{1-2}=7.0 Hz, 1-H), 4.38 (1H, br.t, J_{5a-6}=7.0 Hz, 5a-H), 4.65 (1H, d, J_{2a-2}=9.0 Hz, 2a-H), 5.17 (1H, d, J_{10b-1}=9.8 Hz, 10b-H), 6.08 (1H, br.s, NH, D_2O exchangable), and 6.60—7.92 ppm (14H, m, ArH); MS *m/z* (rel intensity, %) 407 (M^+, 24) and 130 (base peak).

Found: C, 79.37; H, 6.08; N, 10.38%. Calcd for $C_{27}H_{25}ON_3$: C, 79.58; H, 6.18; N, 10.31%.

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