Another Aspect of the Reaction Behavior of Cyclopentadienones: 1,5-Sigmatropic Rearrangement of the 1,4-Addition Products of Amines

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Treatment of 2,5-bis(methoxycarbonyl)-3,4-diphenylcyclopentadienone (**1**) with aniline (**2a**) gave the stereoisomeric 2-anilino-2,5-bis(methoxycarbonyl)-3,4-diphenylcyclopentenones (*cis*- and *trans*-**4a**). ^{1}H NMR spectroscopic monitoring of the reaction indicates that both compounds are derived from the 1,5-sigmatropic rearrangement of the 1,4-addition products *cis*- and *trans*-**3a**. The structure of **3a** was established by the X-ray analysis of the product after methylation (**3a-Enol-Me**) with diazomethane. The sequential pericyclic reaction behavior of **1** with amines is discussed on the basis of X-ray crystal structures and the optimized structure of the transition state at the B3LYP/6–31G(d) level of theory.

Introduction

Cyclopentadienones are powerful 4π-synthons with very low LUMO (lowest unoccupied molecular orbital) energy levels, although there are not many cyclopentadienones existing as monomers. 2,5-Bis(methoxycarbonyl)-3,4-diphenylcyclopentadienone (**1**) does exists in this state, though, and the pericyclic reactions of **1** with various olefins, including medium-sized ring polyenes, have been studied systematically.[1]

During the course of a study of the pericyclic reaction behavior of cyclopentadienones,[2] we found novel cascade reactions[3] in which prop-2-ynylamines added to **1** to give two cyclization products in preference to the Diels−Alder (DA) reaction (Scheme 1). We considered compound **C** to be the intramolecular ene reaction product of the 1,4-addition product (**A**), and compound **D** to have been formed via the 1,5-sigmatropic rearrangement product (**B**) of **A**, followed by an intramolecular DA reaction with the styrene moiety as diene and dehydrogenation of the DA adduct.

On the basis of the structural features of **C** and **D**, we thought that the 1,4-addition product (**A**) should be a common intermediate of both cascade reactions. In connection with these reactions, in order to ascertain the addition reaction behavior of amines toward the cyclopentadienone and the migratory aptitude of the amino groups of the 1,4-addition products, we also studied the reaction between **1** and aniline (**2a**) as a model reaction. ^{1}H NMR monitoring of the progress of the reaction between **1** and **2a** showed the existence of an intermediary compound ascribable as the 1,4-addition product **3a**, which transformed into the 1,5-sigmatropic rearrangement product **4a**.[3a]

The reactions between **1** and amines (**2a**, *o*-phenylenediamine, cyclohexylamine, ethylamine, etc.) had been studied by Eistert et al.[4] In the reaction between **1** and **2a**, these workers unknowingly isolated the 1,4-addition product (**3a**, m.p. 109 °C dec.), which isomerizes to the 1,5-sigmatropic rearrangement product **4a**, and reported that **3a** isomerized to the enol form, the 5-anilino-2-hydroxycyclopentadiene derivative **3a-Enol**, the structure of which was determined by ^{1}H NMR spectroscopy through its methylation product **3a-Enol-Me** with diazomethane (Scheme 2).

Our experimental result is not consistent with their observation in view of the sigmatropic rearrangement behavior of the 1,4-addition product **3a**.

These findings prompted us to reinvestigate the reactions between **1** and **2a** and related amines. The results for the sequential reactions between cyclopentadienones and amines are discussed here in detail on the basis of X-ray crystallographic data and further additional data that we have obtained.

Results and Discussion

We considered the overall reaction pathway for the reaction between **1** and **2a** in terms of frontier molecular orbital (FMO) theory,[5] as a guiding principle for pericyclic reactions. A possible reaction scheme is shown in Scheme 3. There are two modes of the addition reaction: 1,2- (direct) and 1,4- (conjugate) additions of **2a** to **1**. Both primary adducts satisfy the steric requirement of the thermally allowed 1,5-sigmatropic rearrangement of the substituents.

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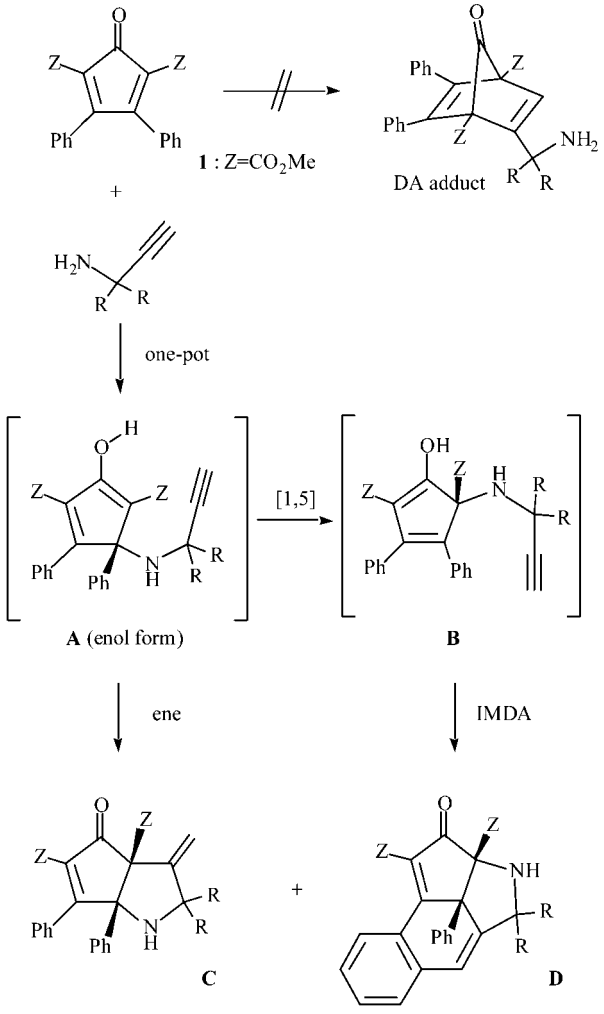
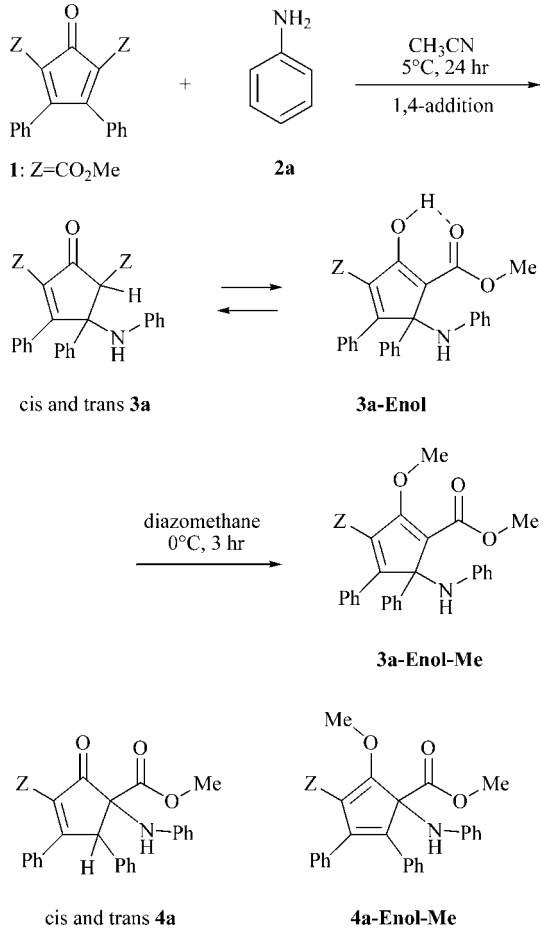


Scheme 1



Scheme 2

As shown in Scheme 3, once **2a** adds to **1**, the anilino group probably migrates to a new position along the cyclopentadiene π system to give a more stable isomer.

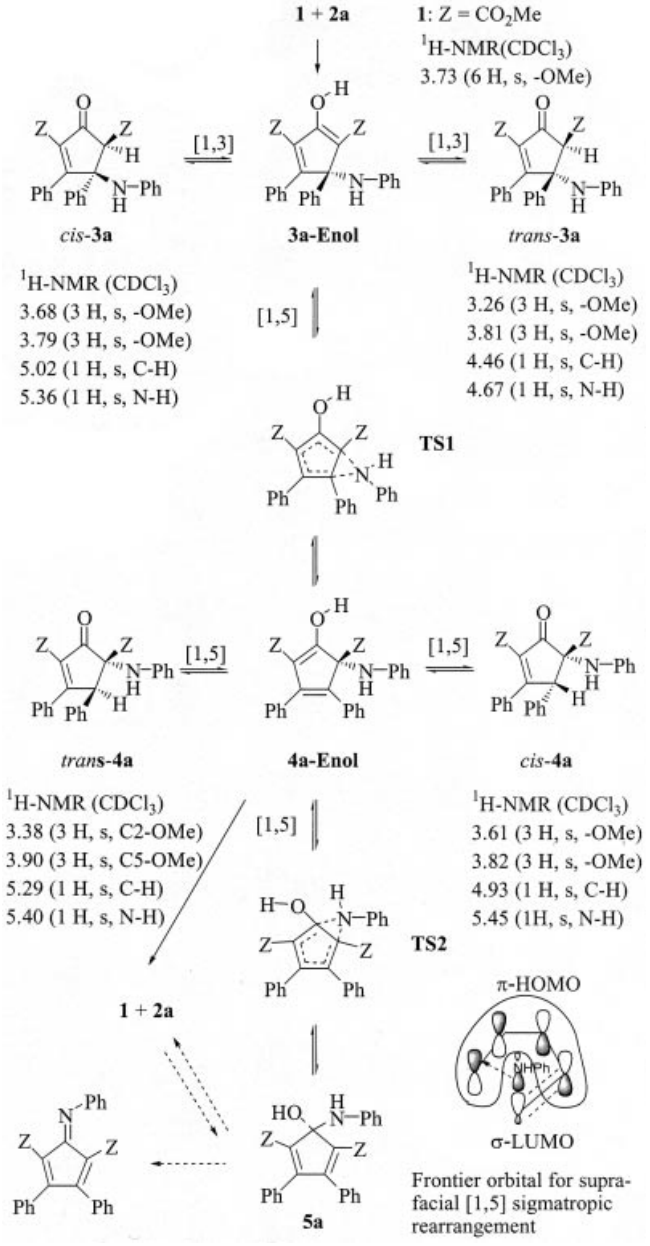
For clarification of the reaction pathway, we reexamined the reaction between **1** and **2a**. A mixture of **1** and **2a** in acetonitrile was allowed to stand at room temperature for 19 h to give a mixture of 1:1 adducts (*trans*-**4a**/*cis*-**4a**, 9:1).

The NMR spectra of both isomers resemble each other very closely except for the chemical shifts of the methoxycarbonyl groups. The methyl protons of a methoxycarbonyl group of *trans*-**4a** showed a high-field shift [δ = 3.38 ppm for CO_2**Me**] in relation to the methyl group [δ = 3.61 ppm for CO_2**Me**] of *cis*-**4a**, implying that the methyl protons of *trans*-**4a** are shielded by the electronic ring current of a neighboring phenyl ring. The ^{1}H NMR and ^{13}C NMR spectroscopic data of the products are not sufficient for determination of the substitution position of the anilino group and its stereochemistry. To clarify the structure of the product, the single-crystal X-ray analysis was undertaken. The crystal data and a computer-generated representation of *trans*-**4a** are shown in Table 1 and Figure 1, respectively. As shown in Figure 1, the product is the 5-anilinocyclopent-2-enone derivative, indicating that the 1,5-sigmatropic rearrangement of the anilino group had taken place even at room temperature. The high-field shift of the methyl protons of the C5-CO_2Me group in the ^{1}H NMR spectrum is attributable to the ring-current effect of the *cis*-oriented phenyl group (C4-Ph).

The single crystal of the stereoisomeric 5-anilinocyclopent-2-enone derivative *cis*-**4a** could be obtained under different reaction conditions. The X-ray structure of *cis*-**4a** is depicted in Figure 2 (see also Table 1).

As can be seen in Figure 1 and 2, the major product is the *trans* isomer (in the spatial orientation of the 4-phenyl and 5-anilino groups), whereas the minor product has a *cis* configuration. In *trans*-**4a**, the NH hydrogen of the anilino group makes a hydrogen bond with the carbonyl oxygen of the CO_2Me group (N−H···O=C 2.310 Å). In the case of *cis*-**4a**, the hydrogen bond is found between the PhN**H** and the enone carbonyl group (N−H···O=C 2.276 Å). The cyclopentenone ring of *cis*-**4a** is considerably distorted, as judged from the dihedral angle (C2−C1−C5−C4 18.9°). This may be due to the presence of the C−H···O= type hydrogen-bond[6] interaction (2.372 Å) between C4−H and the carbonyl oxygen of the C5-CO_2Me group.

On the basis of these results, we tried to isolate the 1,4-addition product **3a**. However, we encountered difficulties



Scheme 3

in the isolation of **3a** in the crystalline state. After some reexamination, we were able to isolate the 1,4 adduct *trans*-**3a** as crystals (m.p. 128 °C) under reaction conditions set up so that the product was separated from the reaction mixture through the use of the least possible amount of solvent at a constant low temperature. Close inspection of the ^{1}H NMR spectrum of the residue of the filtrate indicated the presence of the 1,5-sigmatropic rearrangement products *cis*-**4a** and *trans*-**4a**. The structure of the 1,4-addition product was firmly established by X-ray analysis of the methylated product[4] **3a-Enol-Me**, obtained from treatment with diazomethane (see Figure 3).

A small amount of the methylated enol derivative **4a-Enol-Me** of the 1,5-sigmatropic rearrangement product **4a** was also isolated from the methylation reaction mixture.

Careful monitoring of the progress of the reaction between **1** and **2a** by ^{1}H NMR spectroscopy revealed the overall reaction scheme. A plot of the concentrations of **1**, *cis*-**3a**, *trans*-**3a**, *cis*-**4a**, and *trans*-**4a** against time is depicted in Figure 4, and the ^{1}H NMR assignments of the compounds are shown in Scheme 3.

The configurations of *cis*/*trans*-**3a** with respect to the spatial relationship between the anilino and methoxycarbonyl groups were determined by comparison of the chemical shifts of the methyl protons of the CO_2Me groups of both isomers, the upfield shift being observed in *trans*-**3a** bearing the *cis*-oriented CO_2Me and phenyl groups.

At early stages of the reaction, the concentrations of *trans*-**3a**, *cis*-**3a**, and *cis*-**4a** increased rapidly with the decrease in **1** until maxima were reached and then decreased gradually over time with an increase in *trans*-**4a**. The conversion of *cis*-**4a** into *trans*-**4a** is slower than the others. Inspection of the reaction profile suggests that the 1,4 adduct also involves the *cis* and *trans* isomers.

The ^{1}H NMR spectral changes of the reaction mixture also clarified the presence of the *cis*/*trans* isomerism in both **3a** and **4a**. The *cis*/*trans* isomerism of **3a** is due to keto−enol tautomerism and the isomerism of **4a** presumably originates from the 1,5-sigmatropic rearrangement of the C4-hydrogen to the oxygen atom of the enone group, followed by the reverse reaction. In the reaction, **2a** may act as an organic base to stabilize the enolate form essential for the *cis*/*trans* isomerization of the adducts.

From the experimental results, it becomes clear that the 1,4-addition takes place in preference to the 1,2-addition, in accordance with the known selectivity of amines toward enones.[5] In the 1,5-sigmatropic rearrangement reaction, *cis*-**4a** is considered to be the kinetically controlled product and *trans*-**4a** the thermodynamically controlled product.

To confirm the 1,5-sigmatropic rearrangement, a molecular modeling study was carried out. Density functional theory (DFT)[7] calculations at the B3LYP/6−31G(d) level were performed through the use of the structures optimized by the semiempirical PM3 calculations. The transition state has one negative eigenvalue corresponding to the vibration of the shifting of the anilino moiety from C4 to C5. The transition state (TS1) was further verified by an intrinsic reaction coordinate (IRC) calculation. The N−C4 and N−C5 bond lengths of the three-membered aziridine moiety are 1.677 and 1.624 Å, respectively (see Figure 5).

The B3LYP/6−31G(d)-calculated transition structure for a simple model compound (1,4 adduct of cyclopentadienone and **2a**) showed the N−C4 and N−C5 bond lengths to be 2.260 Å, indicating that the N−C4 and N−C5 bond lengths of TS1 are significantly shortened by the hydrogen bond between the Ph−NH group and the ester carbonyl group, which can be expected from the X-ray structure (PhN−H···O=C< 2.420 Å) of **3a-Enol-Me** (see Figure 3). The bond lengths of the transition structure for the 2-carboxy derivative (1,4 adduct of 2-carboxycyclopentadienone and **2a**) are 1.693 and 1.659 Å, similar to those of TS1. The calculated reaction barrier is 42.5 kcal/mol at B3LYP/6−31G(d) level with ZPE correction, considerably

Table 1. Crystal data and intensity measurement for *trans*-**4a**, *cis*-**4a**, *cis*-**4b**, and **3a-Enol-Me**

Compound	*trans*-**4a**	*cis*-**4a**	**3a-Enol-Me**	*cis*-**4b**
Formula	$C_{27}H_{23}NO_5$	$C_{27}H_{23}NO_5$	$C_{28}H_{25}NO_5$	$C_{29}H_{27}NO_5$
M.p. (C)	175	129	148	175
Molecular weight	441.48	441.48	455.51	469.54
Crystal System	triclinic	monoclinic	triclinic	monoclinic
Lattice Type	primitive	primitive	primitive	primitive
Lattice Parameters				
a (Å)	12.624(3)	17.737(2)	10.252(1)	10.204(4)
b (Å)	20.235(3)	10.409(1)	24.778(4)	15.145(3)
c (Å)	10.668(1)	12.867(2)	9.828(4)	16.339(4)
α (°)	98.84(1)		99.34(1)	
β (°)	94.29(1)	106.13(1)	104.11(1)	106.86(2)
γ (°)	76.96(1)		93.43(1)	
Space Group	$P\bar{1}$ (#2)	*P*21/*a* (#14)	$P\bar{1}$ (#2)	*P*21/*n* (#14)
Z	4	4	4	4
$D_{calcd.}$ (g/cm^3)	1.110	1.285	1.273	1.291
$D_{obsd.}$	1.150	1.287	1.280	1.301
Solvent	EtOH/EtOAc	EtOH/EtOAc	EtOH/EtOAc	EtOH/EtOAc
Scan range		$2\theta < 55.0°$		
Reflections collected	12684	12581	11763	6088
Unique data collected	12133	12130	10920	5551
Unique data used	6363	8889	4858	4108
	$I>3.0\sigma(I)$	$I > 2.0\sigma(I)$	$I > 3.0\sigma(I)$	$I > 3.0\sigma(I)$
R	0.085	0.131	0.088	0.071
Rw	0.137	0.136	0.096	0.134

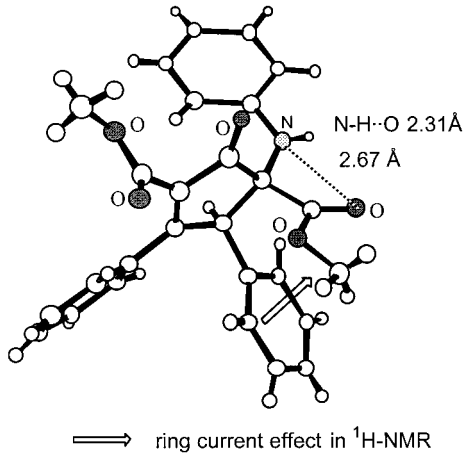


Figure 1. Computer-generated representation of the X-ray structure of *trans*-**4a**; the thermal ellipsoids are omitted for clarity

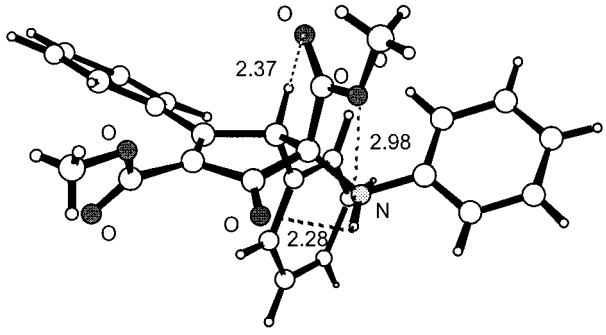


Figure 2. Computer-generated representation of the X-ray structure of *cis*-**4a**; the thermal ellipsoids are omitted for clarity

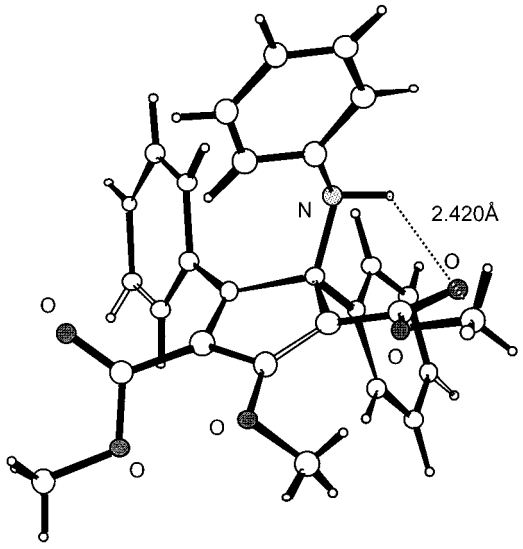


Figure 3. Computer-generated representation of the X-ray structure of **4a-Enol-Me**; the thermal ellipsoids are omitted for clarity

higher than expected from the reaction conditions. To obtain accurate energies, much higher levels of theory seem to be required.

Interestingly, the reaction between **1** and 4-ethylaniline (**2b**) gave the *cis* form (*cis*-**4b**) of the 1,5-sigmatropic rearrangement product of the 1,4 adduct. The crystal structure is depicted in Figure 6. X-ray analysis suggests that the stability of the *cis* isomer may arise from the effective N−H···OMe hydrogen-bond interaction due to the electronic effect of the 4-ethyl group on the aniline ring.

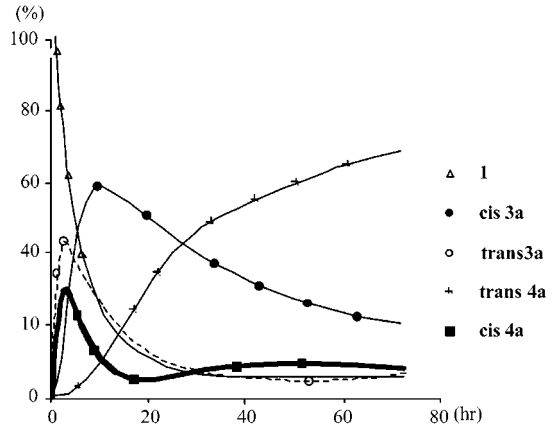


Figure 4. ^{1}H NMR spectroscopic monitoring of the reaction between **1** and **2a**

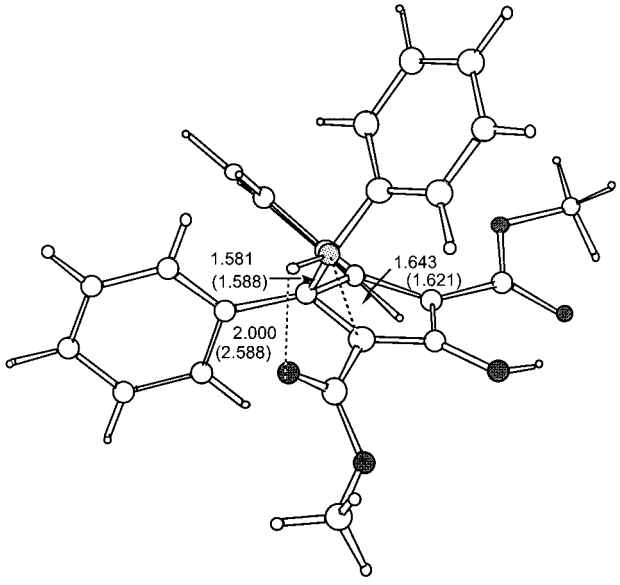


Figure 5. TS geometry of the 1,5-sigmatropic rearrangement of **3a** (enol form) calculated at the B3LYP/6−31G(d) level

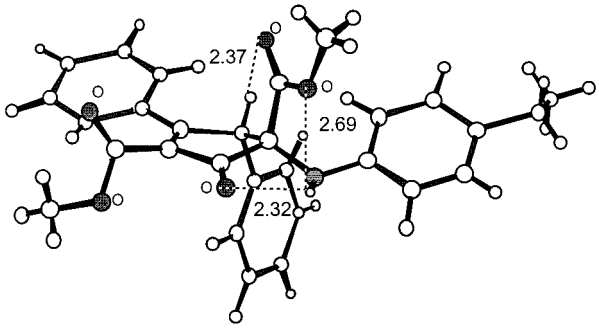


Figure 6. Computer-generated representation of X-ray structure of *cis*-**4b**; the thermal ellipsoids are omitted for clarity

2-Methylaniline (**2c**) gave both *cis* and *trans* adducts **4c**. The introduction of the methyl group at the 2-position of aniline accelerates the decomposition reaction of the adduct.

Aliphatic amines (propyl-, isopropyl-, butyl-, isobutyl- and allylamines) and alcohols (methanol, ethanol) also showed similar reaction behavior, to give the corresponding 1,4 adducts. However, the NMR spectral information could not be obtained because of the facile dissociation to the starting materials in the NMR solvents.

The instability of the 1,5-sigmatropic rearrangement product is primarily the result of a structural feature of the β-keto-α-amino acid (see Figure 7).

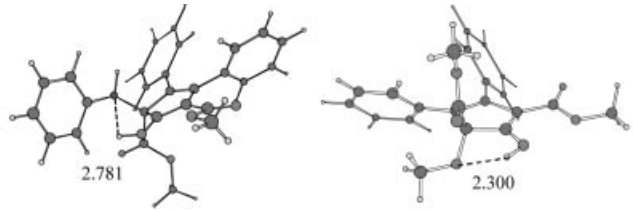


Figure 7. Enol forms of the 1,5-sigmatropic rearrangement products calculated by the DFT method at the B3LYP/6−31G(d) level

The mechanism of the elimination of amines or alcohols is interpreted in terms of the three-system FMO interaction based on the reactant dissection method.[8]

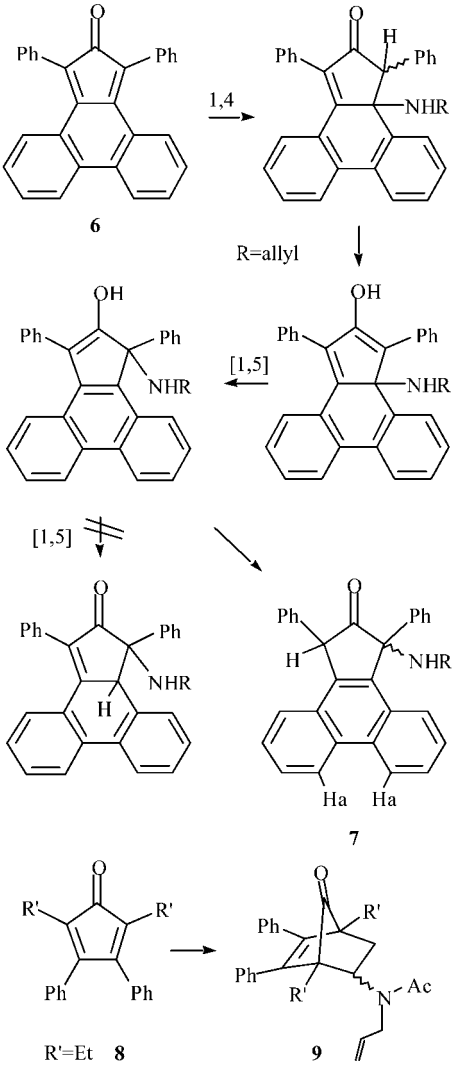
Table 2. Energies of the GS and TS structures for the reaction between **1** and **2a**

Compound	*cis*-**3a**	**3a-Enol**	*trans*-**3a**	**TS1**
PM3[a]	−85.9	−84.8[b]	−86.5	−36.6[b]
B3LYP /6−31G(d)[c]	−1473.5781	−1473.5746 (−1473.1087)[d][e]	−1473.5785	−1473.5030 (−1473.0409)[d,e]
−1473.5781[f]	−1473.4971[f]			
−1473.4880[f]				
Compound	*trans*-**4a**	**4a-Enol**	*cis*-**4a**	
PM3	−87.7	−84.9	−87.7	
B3LYP /6−31G(d)	−1473.5909	−1473.5631	−1473.5920	
−1473.5925[f]				

[a] + Kcal/mol. [b] Reaction barrier 48.2 kcal/mol. [c] Hartree. [d] $E°$, the thermal corrections to energy were scaled by a factor of 0.9804 (298.15°, 1.0 atm). [e] Reaction barrier 42.5 kcal/mol. [f] Values for conformational isomers due to rotation around the C−CO_2Me bonds.

An alternative reaction pathway for the elimination of aniline is possible: compound **4** might undergo a 1,5-sigmatropic rearrangement to give the 1,2-addition product (i.e., the hemiaminal, **5**).[9] However, we can rule out this reaction pathway since we were unable to observe any ^{1}H NHR signals attributable to the symmetric structure of **5a**.

The reaction between phencyclone (**6**) and allylamine gave the 2-allylamino-3-cyclopentenone derivative **7**, which may be formed by the proposed reaction mechanism and stabilized by the recovery of aromaticity in the phenanthrene ring (see Scheme 4).



Scheme 4

The reaction between 2,5-diethyl-3,4-diphenylcyclopentadienone (**8**) and diallylamine, which had reacted with **1** to afford the cascade reaction product,[3] did not give the 1,4-addition product but instead gave the corresponding DA adducts **9**.

In the reactions between **1** and primary and secondary amines, perceptible transient color changes (orange → green) were observed in the reaction mixture at an early stage of the reaction. The ^{1}H NMR spectrum of the reaction mixture (e.g., **1** + dipropylamine) at an early stage showed broadening of the methoxy and phenyl signals due to complex formation. Use of tertiary amines (e.g., triethylamine) did not produce similar transient color changes with **1**. The hydrogen bonding to the carbonyl groups of **1** lowers the LUMO energy level (E_{LUMO} −1.88 eV → −2.11 eV), resulting in an enhancement of the electron-accepting ability favorable for donor−acceptor interaction between addends. On the other hand, 2,5-diethyl-3,4-diphenylcyclopentadienone (**8**; E_{LUMO} = −1.11 eV) did not show coloration to give the DA adduct. These indicate that 1,4-addition of amines to **1** might be affected by charge-transfer complex formation.[10] In the cascade reactions between **1** and unsaturated amines, the *n*-HOMO (lone pair electron) of amines lying above the π-HOMO (NHOMO) of the unsaturated bond acting as a 2π-source in the DA reaction plays a crucial role interacting with the π-LUMO of **1**, leading to the 1,4-addition reaction followed by the sequential pericyclic reactions.

Conclusion

In conclusion, the reaction between **1** and **2a** gave the 1,4-addition product, which then rearranges to give the 1,5-sigmatropic rearrangement product. The structures of the 1,4 adduct and the 1,5-sigmatropic rearrangement products were verified by single-crystal X-ray analysis. The detailed analysis of ^{1}H NMR monitoring revealed the existence of the 1,5-sigmatropic rearrangement of the 1,4-addition product. This investigation strongly supports the assumption that the 1,4-addition product plays a key role as a common intermediate in the cascade reactions between prop-2-ynylamines and the cyclopentadienone. Electron-deficient cyclopentadienones, in conjunction with the use of the 4π-synthon, are potential enone components for the skeletal construction of heterocycles.

On the basis of this study, we are currently investigating the cascade reactions between cyclopentadienones and prop-2-yn-1-ols in the presence of tertiary amines.

Experimental Section

General: Melting points were uncorrected. The IR spectra were taken with a Hitachi 270−30 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were taken with JEOL JNM-EX 270 (270 MHz), JNM-AL 300 (300 MHz), and JNM-A 500 (500 MHz) spectrometers on ca. 10% solutions with TMS as an internal standard; chemical shifts are expressed as δ values and the coupling constants (*J*) are expressed in Hz. Mass spectra were obtained with JEOL JMS-DX 303 and JEOL JMS-BU20 (GCmate) instruments. UV spectra were recorded with a Shimadzu UV-2500PC spectrophotometer.

Materials: 2,5-Bis(methoxycarbonyl)-3,4-diphenylcyclopentadienone (**1**),[11a] phencyclone (**6**),[11b] and 2,5-diethyl-3,4-diphenylcyclopentadienone (**8**)[11a] were prepared by the previously reported method.

Reaction between 1 and Aniline (2a): A mixture of **1** (500 mg, 1.4 mmol) and **2a** (300 mg, 3.2 mmol) in acetonitrile (8 mL) was

stirred at room temperature for 3 days. After evaporation of the solvent, the residue was chromatographed over silica gel with a benzene/EtOAc mixture (20:1) as eluent to give the 1,5-sigmatropic rearrangement product *trans*-**4a** (581 mg, 90%) and *cis*-**4a** (72 mg, 10%).

Isomer *trans*-4a: Yellow prisms, m.p. 129 °C. IR (KBr): $\tilde{\nu}$ = 3368 (>NH), 1758, 1734, 1710 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.38 (s, 3 H, $COOCH_3$), 3.90 (s, 3 H, $COOCH_3$), 5.29 (s, 1 H, methine), 5.40 (s, 1 H, NH), 6.59−7.40 (m, 15 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 52.0, 52.5 ($COOCH_3$ × 2), 52.8 (>CH−), 75.0 (>*C*(NH−Ph)$COOCH_3$), 142.6 (>C=*C*−$COOCH_3$), 164.4 (C=*C*−Ph), 167.8, 170.3, 196.0 (>C=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 441 (62) [M^+], 382 (100), 350 (23), 247 (74). The stereochemistry was established by X-ray analysis.

Isomer *cis*-4a: Yellow crystal; m.p. 175 °C. IR (KBr): $\tilde{\nu}$ = 3368 (>NH), 1716 (br. C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.62 ppm (s, 3 H, $COOCH_3$), 3.82 (s, 3 H, $COOCH_3$), 4.93 (s, 1 H, NH), 5.45 (s, 1 H, methine), 6.42−7.41 (m, 15 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 52.5, 53.9 ppm ($COOCH_3$ × 2), 59.0 (>CH−), 77.5 (>*C*(NH−Ph)$COOCH_3$), 134.4 (>C=*C*−$COOCH_3$), 144.5 (C=*C*−Ph), 169.6, 178.3, 195.1 (>C=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 441 (56) [M^+], 382 (100), 350 (18), 247 (80). The stereochemistry was established by X-ray analysis.

Isolation and Identification of 3a (Reinvestigation of the Previous Reports): A mixture of **1** (2.5 g, 7.0 mmol) and **2a** (1.5 g, 16.0 mmol) in acetonitrile (40 mL) was stirred at 5 °C for 24 h. The precipitates were collected and washed with cold diethyl ether. The product was dried in vacuo to give a yellow powder (*trans*-**3a**, 1.9 g, 60%). After the filtrate had been evaporated to dryness, the residue was chromatographed over silica gel with a benzene/EtOAc mixture (30:1) as eluent to give the 1,5-sigmatropic rearrangement products *cis*-**4a** (70 mg, 2.2%) and *trans*-**4a** (202 mg, 6.4%).

Compound *trans*-3a: Yellow powder; m.p. 128 °C. IR (KBr): $\tilde{\nu}$ = 3436 (>NH), 1750, 1732, 1704 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.26 ppm (s, 3 H, $COOCH_3$), 3.81 (s, 3 H, $COOCH_3$), 4.46 (s, 1 H, methine), 4.67 (s, 1 H, NH), 6.70−7.54 (m, 15 H, ArH) ppm. MS (FAB): *m*/*z* (%) = 442 (24) [M^+ + 1], 441 (11) [M^+], 307 (37), 154 (100), 136 (57). $C_{27}H_{23}NO_5$ (441.46): calcd. C 73.46, H 5.25, N 3.17; found C 73.75, H 5.14, N 3.27.

When the ^1H NMR sample solution was allowed to stand at room temperature, *trans*-**3a** gradually transformed into a mixture of **3a**, **4a**, and **1a**.

Reaction between *trans*-3a and Diazomethane: A mixture of *trans*-**3a** (500 mg, 1.1 mmol) in MeOH (3 mL) and diazomethane in diethyl ether (40 mL; a solution of diazomethane in diethyl ether was prepared from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (4.3 g) (by the established method) was stirred at 0 °C for 3 h. The precipitated crystals were collected and washed with cold diethyl ether. The product was dried under vacuum to give a yellow powder (**3a-Enol-Me**, 350 mg, 68%). After the filtrate had been evaporated to dryness, the residue was chromatographed over silica gel with a benzene/EtOAc mixture (3:1) as eluent to give the 1,5-sigmatropic rearrangement product **4a-Enol-Me** (14 mg, 2.7%).

Compound 3a-Enol-Me: Yellow prisms, m.p. 148 °C. IR (KBr): $\tilde{\nu}$ = 3392, 3356 (>NH), 1724, 1676 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.53 ppm (s, 3 H, $COOCH_3$), 3.68 (s, 3 H, OCH_3), 4.09 (s, 3 H, $COOCH_3$), 4.74 (s, 1 H, NH), 6.79−7.36 (m, 15 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 51.1 ppm ($COOCH_3$), 52.1 (C2-OCH_3), 62.4 ($COOCH_3$), 75.8 [>C(NH−Ph)Ph], 113.2, 130.3, 160.0 (C=*C*−Ph), 162.5, ($COOCH_3$), 164.7, 166.8 ($COOCH_3$) ppm. MS (EI, 70 eV): *m*/*z* (%) = 445 (24) [M^+], 423 (100), 396 (34), 363 (97). $C_{28}H_{25}NO_5$ (455.50), calcd. C 73.83, H 5.53, N 3.08; found C 73.61, H 5.47, N, 3.09. The ^1H NMR spectroscopic data are essentially identical to the previously reported data.[4] The structure was established by the X-ray analysis.

Compound 4a-Enol-Me: Orange oil. IR (KBr): $\tilde{\nu}$ = 3396 (>NH), 1734, 1666 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.47 [s, 3 H, C(NH−Ph)$COOCH_3$), 3.67 (s, 3 H, C−OCH_3), 3.94 (s, 3 H, CO-OCH_3), 4.48 (s, 1 H, NH), 6.26−7.35 (m, 15 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 52.0 ppm (−OCH_3), 54.4 [C(NH−Ph)$COOCH_3$), 63.3 ($COOCH_3$), 71.5, 98.6, 164.3 [C(NH−Ph)$COOCH_3$), 164.7 ($COOCH_3$) ppm. MS (FAB): *m*/*z* (%) = 456 (46) [M^+ + 1], 455 (10) [M^+], 424 (53), 363 (100). The previously reported spectroscopic data for *cis*-**3a** should be reassigned as for *cis*-**4a**. The formation of *trans*-**3a** was only recognized in the ^1H NMR spectrum of the reaction mixture by analysis of data behavior in comparison with those of the related compounds. The peak assignments are shown in Scheme 3.

Adducts of 1- and 4-Ethylaniline (2b) and 2-Methylaniline (2c): The following compounds were obtained by essentially the same procedure as above; *cis*-**4b** (410 mg, 61%) from **2b**, and *cis*-**4c** (76 mg, 12%) and *trans*-**4c** (15 mg, 2.3%) from **2c**.

Compound *cis*-4b: Orange crystals, m.p. 175 °C. IR (KBr): $\tilde{\nu}$ = 1712, 1730 (C=O), 3392 (>NH) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.12 ppm (t, *J* = 7.5 and 7.7 Hz, 3 H, CH_3), 2.47 (q, *J* = 7.5 Hz, 2 H, CH_2), 3.57 (s, 3 H, $COOCH_3$), 3.78 (s, 3 H, $COOCH_3$), 4.85 (s, 1 H, NH), 5.44 (s, 1 H, methine), 6.35−7.43 (m, 14 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 15.6 ppm (−CH_3), 27.7 (−CH_2), 52.3, 53.7 ($COOCH_3$ × 2), 59.0 (>CH−), 77.0 (>*C*(NH−Ph)$COOCH_3$), 142.2 (>C=*C*−$COOCH_3$), 163.5 (C=*C*−Ph), 169.7, 178.1, 195.2 (>C=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 469 (55) [M^+], 410 (100), 247 (68). $C_{29}H_{27}NO_5$ (469.53): calcd. C 74.18, H 5.80, N, 2.98; found C 73.89, H 5.75, N 2.92. The stereochemistry was established by the X-ray analysis.

Compound *trans*-4c: Yellow crystals, m.p. 145 °C. IR (KBr)): $\tilde{\nu}$ = 1752, 1728, 1700 (C=O), 3424 (>NH) cm^{-1}. ^1H NMR($CDCl_3$): δ = 2.00 (s, 3 H, CH_3), 3.18 (s, 3 H, $COOCH_3$), 3.65 (s, 3 H, $COOCH_3$), 4.32 (s, 1 H, NH), 4.62 (s, 1 H, methine), 6.92−7.35 (m, 14 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 15.6 ppm (−CH_3), 50.5, 50.6 ($COOCH_3$ × 2), 65.2 (>CH−), 68.2 (>*C*(NH−Ph)$COOCH_3$), 140.1 (>C=*C*−$COOCH_3$), 160.9 (C=*C*−Ph), 164.9, 179.4, 193.6 (>C=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 456 (36) [M^+ + 1], 391 (22), 349 (67), 257 (39), 107 (97), 44 (100). $C_{28}H_{25}NO_5$ (455.50): calcd. C 73.83, H 5.53, N, 3.08; found C 73.77, H 5.68, N 2.87.

Compound *cis*-4c: Orange crystals, m.p. 165 °C. IR (KBr)): $\tilde{\nu}$ = 1724 (br. due to three carbonyls), 3440 (>NH) cm^{-1}. ^1H NMR($CDCl_3$): δ = 1.91 ppm (s, 3 H, CH_3), 3.60 (s, 3 H, CO-OCH_3), 3.79 (s, 3 H, $COOCH_3$), 5.47 (s, 1 H, methine), 4.80 (s, 1 H, NH), 7.30−7.42 (m, 14 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 17.0 ppm (−CH_3), 52.3, 53.8 ($COOCH_3$ × 2), 58.7 (>CH−), 77.3 (>*C*(NH−Ph)$COOCH_3$), 142.3 (>C=*C*−$COOCH_3$), 163.4 (C=*C*−Ph), 169.8, 170.9, 195.4 (>C=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 455 (56) [M^+], 396 (100), 247 (88), 91 (47). $C_{28}H_{25}NO_5$ (455.50): calcd. C 73.83, H 5.53, N 3.08; found C 74.08, H 5.75, N 2.99.

Reaction between Phencyclone (6) and Allylamine: The adduct was obtained by the method described above, from phencyclone (3.8 g, 10 mmol) and allylamine (1.1 g, 20 mmol) in 1,4-dioxane (10 mL).

The precipitates were washed with diethyl ether to give the adduct **7** (2.4 g, yield 55%). **7**: Colorless crystals, m.p. 210−212 °C. IR (KBr): $\tilde{\nu}$ = 1752 (C=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.86 ppm (dd, *J* = 12.8 and 6.7 Hz, 1 H, >CH-*H*), 2.99 (dd, *J* = 4.9 and 12.8 Hz, 1 H, >CH−*H*), 4.98 (dd, *J* = 10.4, 1 H, =CH*H*−), 5.09 (dd, *J* = 17.1, 1 H, =CH*H*), 5.84 (dd, *J* = 10.4 and 17.1 Hz, 1 H, -C*H*=CH_2), 5.25 [s, 1 H, C*H*(Ph)], 7.13−7.67 (m, 16 H, aromatic H), 8.74 (d, *J* = 8.6 Hz, 1 H, Ha), 8.76 (d, *J* = 8.6 Hz, 1 H, Ha) ppm. ^{13}C NMR (125 MHz $CDCl_3$): δ = 47.8 ppm (−*C*H_2 C=CH_2), 56.5 [−*C*H(Ph)], 76.1 [−*C*(NH)Ph], 116.0 (CH=*C*H_2), 122.9, 123.4, 125.9, 126.2, 126.8, 127.2, 127.4, 127.6, 128.1, 128.6, 128.8 (Ar CH), 128.2, 128.4, 131.1, 131.7, 135.0, 136.5, 136.6, 140.2 (Ar-C), 215.2 (C=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 411 (18) [M^+ − CO], 382 (92), 370 (100), 354 (80). $C_{32}H_{25}NO$ (439.19), calcd. C 87.44, H 5.73, N 3.19; found C 87.54, H 5.67, N 3.24.

Reaction between 2,5-Diethyl-3,4-diphenylcyclopentadienone (8) and Diallylamine: A solution of **8** (500 mg, 1.7 mmol) and diallylamine (500 mg, 5.2 mmol) in benzene (2 mL) was heated at reflux for 8 h. After evaporation of benzene, the residue was treated with Ac_2O (0.6 mL) in pyridine (2 mL). The reaction mixture was poured onto ice water. The oil was extracted with diethyl ether. The diethyl ether layer was washed with dil. HCl and then with water. After evaporation of diethyl ether, the residue was purified by chromatography on silica gel to give the DA adducts as the acetyl derivatives [*endo*-**9** (193 mg, 26%) and *exo*-**9** (82 mg, 11%)].

Isomer *endo*-9: Colorless crystals, m.p. 110−113 °C. IR (KBr): $\tilde{\nu}$ = 1770 (bridge C=O), 1646 (>C=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.74 ppm (t, *J* = 7.3 Hz, 3 H, −CH_2−C*H*$_3$), 0.95 (t, *J* = 7.3 Hz, 3 H, −CH_2−C*H*$_3$), 1.64 −1.72 (m, 3 H, 2-*H*β and −C*H*$_2$−CH_3), 1.81−1.89 (m, 1 H, −C*H*H−CH_3), 2.09 (s, 3 H, CO−CH_3), 2.06−2.14 (m, 1 H, 2-Hα), 2.73−2.77 (m, 1 H, 3-H), 2.99 (dd, *J* = 4.3 and 12.8 Hz, 1 H, >CH−CH−N), 3.77 (dd, *J* = 17.7 and 4.9 Hz, 1 H, N−CH*H*−CH=), 3.90 (dd, *J* = 17.7 and 4.9 Hz, 1 H, N C*H*H,−CH=), 4.02 (dd, *J* = 11.0 and 12.8 Hz, 1 H, >CH−C*H*H−N), 5. 12 (d, *J* = 17.7 Hz, 1 H, −CH=CH*H*), 5.20 (d, *J* = 10.4 Hz, 1 H, −CH=C*H*H), 5.68−5.75 (m, 1 H, −C*H*=CH_2), 7.32−6.98 (m, 10 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.0, 9.2, 18.9, 19.4, 21.5, 32.6, 36.5, 47.7, 51.2, 56.5, 58.9, 116.8, 132.7, 140.5, 145.1, 171.5, 206.0 ppm. MS (EI, 70 eV): *m*/*z* (%) = 427 [M^+]. $C_{29}H_{33}NO_2$ (427.58): calcd. C 81.46, H 7.78, N 3.28; found C 81.34, H 7.71, N 3.34.

Isomer *exo*-9: Colorless crystals, m.p. 133−136 °C. IR (KBr): $\tilde{\nu}$ = 1752 (bridge C=O), 1652 (>C=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.58 ppm (t, *J* = 7.3 Hz, 3 H, −CH_2−C*H*$_3$), 0.77 (t, *J* = 7.3 Hz, 3 H, −CH_2−C*H*$_3$), 1.63−1.69 (m, 2 H, 2-Hβ and −C*H*H−CH_3), 1.76−1.88 (m, 4 H, 2-*H*α and −CH_2C*H*$_3$), 2.11 (s, 3 H, −$COCH_3$), 2.67−2.71 (m, l H, 3-H), 3.30 (t, *J* = 12.8 Hz, 1 H, >CH−CH*H*−N), 3.52 (dd, *J* = 4.3 and 12.8 Hz, 1 H, >CH−C*H*H−N), 3.93 (dd, *J* = 17.7 and 4.9 Hz, 1 H, N−CH*H*−CH=), 4.02 (dd, *J* = 17.7 and 4.9 Hz, 1 H, N−C*H*H−CH=), 5.18 (d, *J* = 17.1 Hz, 1 H, −CH=CH*H*), 5.25 (d, *J* = 10.4 Hz, 1 H, CH=C*H*H), 5.78−5.83 (m, 1 H, −C*H*= CH2), 7.01−7.28 (m, 10 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.1, 16.6, 19.6, 21.9, 33.3, 38.7, 47.9, 52.3, 55.7, 58.9, 116.9, 135.5, 142.8, 144.7, 170.3, 207.9 ppm. MS (EI, 70 eV): *m*/*z* (%) = 427 [M^+]. $C_{29}H_{33}NO_2$ (427.58): calcd. C 81.46, H 7.78, N 3.28; found C 81.19, H 7.82, N 3.45.

^1H NMR Monitoring of the Reaction between 1 and 2a: A solution of **1** (500 mg) and **2a** (300 mg) in MeCN (8.0 mL) was prepared. At a given temperature, the ensuing reaction was monitored by analysis of the ^1H NMR signals of the OCH_3 groups of **1** and the reaction products, the chemical shifts of which are listed in Scheme 3. A graphical representation of the changes of the concentrations is depicted in Figure 4.

X-ray Crystallographic Study: Single crystals of the compound *cis*-**4a** were prepared by slow evaporation of an ethanol/ethyl acetate solution at room temperature. The cell constants were found by a least-squares procedure with use of the values of the Bragg angles of 20 reflections. Systematic absences of reflections indicate the space group to be *P*21/*a* (No. 14). All measurements were made on a Rigaku AFC-7 four-circle autodiffractometer with graphite monochromated Mo-K_α radiation. The reflection data were collected by the ω-2θ scan technique to a maximum 2θ value of 55.0°. Of the unique reflections measured, reflections with $I_o > 2.00\sigma(I)$ were used. The structures were solved by direct methods.[12] The non-hydrogen atoms were refined anisotropically and the hydrogen atoms were refined isotropically. Some methoxycarbonyl group hydrogens were located on calculated positions and refined. Full-matrix, least square refinement was used and the unweighted (*R*) and weighted agreement factors (*Rw*) are given.

Neutral atom scattering factors were taken from the International Tables for X-ray Crystallography.[13] All calculations were performed on a Silicon Graphics O2 workstation with teXsan Crystal Structure Analysis Package.[14]

The crystal structures of *trans*-**4a**, **3a**-**Enol-Me**, and *cis*-**4b** were solved similarly. The numbering schemes used in this paper and ORTEP representations are listed in the Supporting Information (see also the footnote on the first page of this article). CCDC-212296 to -212299 for *trans*-**4a**, *cis*-**4a**, **3a**-**Enol-Me**, and *cis*-**4b** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) + 44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk].

Computational Details: Semiempirical MO calculations were run through the CS Chem3D Pro interface with the aid of MOPAC97 on a Macintosh G4 personal computer (dual CPU). The ground-state (GS) structures were optimized by the EF routine implemented in the MOPAC program packages by use of the MNDO-PM3 (PM3) approximation. The transition states (TS) were located by the transition state location routine. The fully optimized geometries calculated by the PM3 method were used as starting geometries for the ab initio and DFT calculations.

DFT calculations were carried out at the B3LYP/6−31G(d) level of theory by use of the Linda Gaussian 98 package[7] on a PC (Pentium 4, 3.0 MHz) cluster of four processors. Geometry optimizations were undertaken with default convergence limits. Transition structures were located by use of the TS keyword. Vibrational frequencies were used to characterize the nature of the stationary points and to obtain thermodynamic parameters. Zero-point energy (ZPE) corrections were scaled by 0.9804.[15] Graphical analysis of the MO calculation data was performed on a Macintosh G4 personal computer.

The DFT calculation data (Cartesian coordinates) are also available from our laboratory web site (http://yakko.pharm.kumamoto-u.ac.jp/).

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[9] The LUMO coefficients of **1** indicate that the largest coefficient is located at the C3 position, favorably for the 1,4-addition reaction. If the 1,2-addition product is formed, the initial *N*-phenyl-substituted hemiaminal may lose water to give the stable Schiff base.

[10] The AM1-calculated FMO energy levels (eV) are as follows: **1**, LUMO −1.88, HOMO −9.65; **6**, LUMO −1.60, HOMO −8.42; **8**, LUMO −1.11, HOMO −8.90.

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