



RRPA91080064 (13.P)

行政院國家科學委員會專題研究計畫。 成不報百

8-Aryl-8-azaheptafulvenes: Tropone 的一很不錯的
“前驅替代物”和給電子基取代之 Fulvenes
進行 [m+n] 環化加成反應之研究

計畫類別： 個別型計畫

計畫編號： NSC - 91 - 2113 - M - -034 - 003

執行期限： 91 年 8 月 1 日 至 92 年 7 月 31 日

執行單位： 中國文化大學，化學系

計畫主持人： 劉清揚

報告類型： 精簡報告

處理方式： 本計畫可公開查詢

中 華 民 國 92 年 10 月 15 日



Pergamon

Stereoselectivity, periselectivity, and regioselectivity in the cycloadditions of 8-(*p*-chlorophenyl)-8-azaheptafulvene with cyclopentadiene and fulvenes

Ching-Yang Liu,* Chi-Chang Chen, Yu-Jui Shie, Lu-Wei Chung, Tzong-Shing Cheng, Ming-Ying Shie, Sheng-Yau Lin and Yueh-Lun Tsai

Institute of Applied Chemistry, Chinese Culture University, Hwa Kang, Taipei 111, Taiwan, ROC

Received 30 December 2002; revised 20 May 2003; accepted 16 June 2003

Dedicated to Professor K. N. Houk, an inspiring teacher and scholar to whom we are very grateful

Abstract—The stereoselectivity, periselectivity, and regioselectivity in the cycloaddition reactions of 8-(*p*-chlorophenyl)-8-azaheptafulvene with cyclopentadiene and symmetrical/unsymmetrical fulvenes is described.

© 2003 Elsevier Ltd. All rights reserved.

1. Introduction

The competition among thermally allowed [4+2], [6+4], and [8+2] cycloaddition reactions has prompted much investigation. It is well known that tropone (**1**) reacts with cyclopentadiene (**2**) stereoselectively and periselectively to give the *exo*-[6+4] cycloadduct **3** (Scheme 1(a)).^{1,2} By contrast, Machiguchi et al. reported that trophothione (**4**), a sulphur analog of tropone, reacts with **2** to afford the *endo*-[8+2] cycloadduct **5** (Scheme 1(b)).^{3,4} Interestingly, Kitahara and Oda reported that 8,8-dicyanoheptafulvene (**6**), a carbon analog of tropone, reacts with **2** to afford the *exo*-[6+4] cycloadduct **7**, which undergoes a [3,3] sigmatropic shift to yield the [8+2] cycloadduct **8**, which in turn mainly reverts back to starting materials **6** and **2** at higher temperatures, which finally recombine to form the thermodynamically most stable [4+2] cycloadducts **9** (Scheme 1(c)).⁵

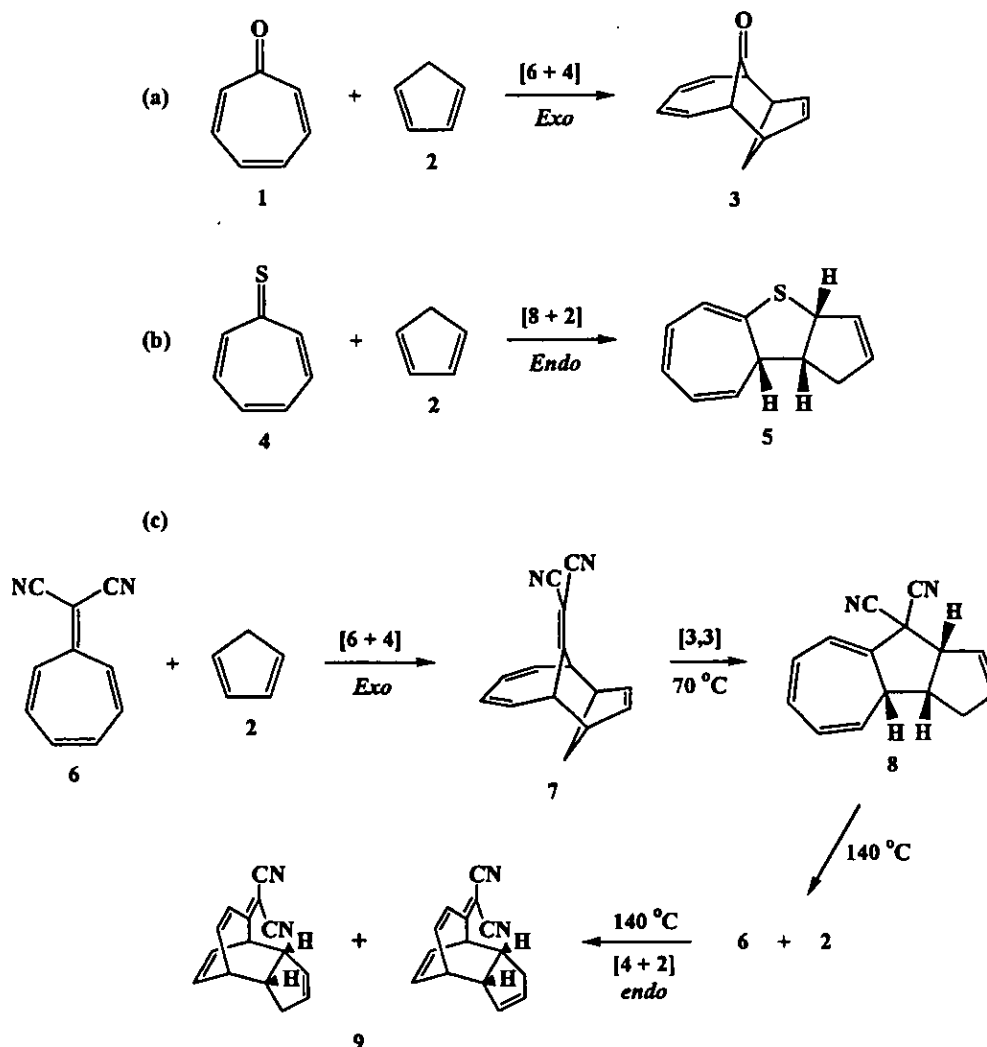
Houk et al. reported the periselective formation of 1:1 [6+4] cycloadducts **11a–c**, respectively, in the cycloaddition reactions of tropone (**1**) with electron-rich substituted 6-methyl- (**10a**), 6-phenyl- (**10b**), and 6,6-dimethyl- (**10c**) fulvenes, which immediately undergo 1,5-sigmatropic hydrogen shifts to yield the thermodynamically more stable cyclopentadienes **12**, which subsequently undergo a second

[6+4] cycloaddition with **1** to form 2:1 cycloadducts **13a–c**, respectively (Scheme 2(a)).^{6–8} A trace of [4+2] cycloadduct **14c** was also obtained. By contrast, Sasaki et al. reported that tropone (**1**) reacts with more hindered 6,6-diphenylfulvene (**10d**) to afford only [4+2] cycloadduct **14d** instead of the expected [6+4] cycloadduct (Scheme 2(b)).⁹ The behaviors of these cycloaddition reactions seem to indicate sensitivity to steric requirements of the exocyclic substituents on the fulvenes. However, in the cycloaddition reactions of trophothione (**4**) with fulvenes **10c** and **10d**, only [8+2] cycloadducts **15c** and **15d** were obtained, respectively (Scheme 2(c)).¹⁰ No [6+4] or [4+2] cycloadduct was isolated. We have reported that electron-deficient 8,8-dicyano- (**6a**: R¹=R²=CN) and 8,8-bis(methoxycarbonyl)- (**6b**: R¹=R²=CO₂Me) heptafulvenes react with 6,6-dimethylfulvene (**10c**: R³=R⁴=Me) and 6,6-diphenylfulvene (**10d**: R³=R⁴=Ph) to give *anti*-endocyclic [8+2], *anti*- and/or *syn*-endocyclic [4+2], and/or *anti*-[6+4] cycloadducts (Scheme 3).¹¹ We proposed that the *endo* stereochemistry of these reactions is controlled by secondary orbital interactions, and the preferred *anti* regioselectivity (R¹/R² vs. R³/R⁴) could be attributed to the steric repulsion between the exocyclic substituents on the heptafulvenes and fulvenes. We have also found that in the unsymmetrical cycloadditions of heptafulvenes with fulvenes, the exocyclic substituent effects exert controlling influence upon the periselectivity and regioselectivity of these cycloadditions (Scheme 3).^{12,13}

In this paper, we report the cycloaddition reactions of 8-(*p*-chlorophenyl)-8-azaheptafulvene (**16**), a nitrogen analog of tropone, with cyclopentadiene (**2**) (Scheme 4) and

Keywords: 8-(*p*-chlorophenyl)-8-azaheptafulvene; fulvenes; cyclopentadiene; stereoselectivity; periselectivity; regioselectivity; [4+2] and [6+4] cycloadditions.

* Corresponding author. Tel.: +86-8862-2713-7869; fax: +86-8862-2713-8969; e-mail: liuchingyang1957@yahoo.com.tw



Scheme 1.

symmetrically- and unsymmetrically-substituted fulvenes 10c–f (Schemes 5–8).

2. Results and discussion

2.1. Reactions of 8-(*p*-chlorophenyl)-8-azaheptafulvene (16) with cyclopentadiene (2) (Scheme 4)

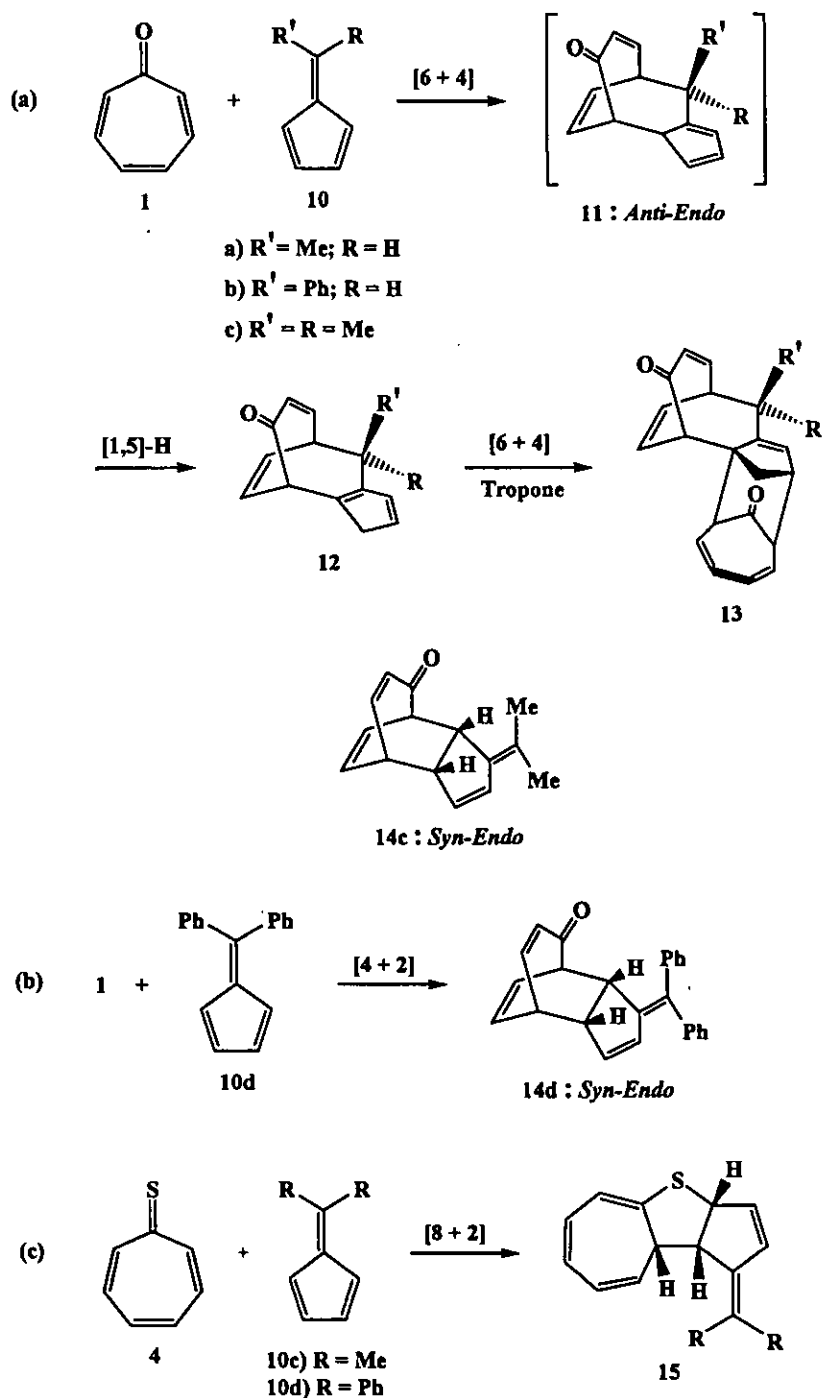
The reaction of 8-(*p*-chlorophenyl)-8-azaheptafulvene (16) with cyclopentadiene (2) at room temperature for 24 h gave an *exo*-[6+4] cycloadduct 17 in 35% isolated yield (Scheme 4). The ^1H NMR spectrum showed six aliphatic protons, six olefinic protons, and four aromatic protons. The methylene protons resonated at δ 1.37–1.42 (m, H-11) and 2.10 (d, H-11'). The bridgehead protons resonated at δ 2.81–2.83 (m, H-1), 2.98–2.99 (m, H-4), 3.25–3.28 (m, H-10), and 3.34–3.37 (m, H-5). The olefinic protons showed five signals at δ 5.56 (bdd, H-9), 5.81 (dd, H-2), 5.94 (bdd, H-6), 5.98–6.02 (m, H-7 and H-8), and 6.05 (dd, H-3). The aromatic ring protons gave two signals at δ 6.50 (d, 2H, Ph) and 7.15 (d, 2H, Ph'). Extensive analysis of 2D ^1H – ^1H COSY and NOESY spectra of 17 established the structure shown in Figure 1. The NOE correlations in the

NOESY spectrum, H-11' to H-6, H-7, H-8, and H-9, H-11 to H-1, H-2, H-3, and H-4, H-10 to Ph, and Ph to H-10, H-2, and H-9 as shown in Figure 1, confirmed the *exo* stereochemistry of this cycloadduct.

Unfortunately, the attempted hydrolysis reaction of cycloadduct 17 to 3 and [3,3] sigmatropic rearrangement to the expected [8+2] cycloadduct 18 were unsuccessful (Scheme 4), with mainly the starting material 17 being recovered.

2.2. Reactions of 8-(*p*-chlorophenyl)-8-azaheptafulvene (16) with symmetrically substituted 6,6-dimethylfulvene (10c) (Schemes 5 and 6)

8-(*p*-Chlorophenyl)-8-azaheptafulvene (16) reacted sluggishly with 6,6-dimethylfulvene (10c) in chloroform at room temperature over 24 h to give an *anti-endo*-[6+4] cycloadduct 20c in 10% isolated yield (Scheme 5 and Table 1). When the reaction of 16 and 10c was carried out in refluxing benzene for 12 h, the cycloadduct 20c was obtained in much higher yield (56%, Scheme 5 and Table 1). Cycloadduct 20c must arise from an initial [6+4] cycloaddition that forms 19c followed by a



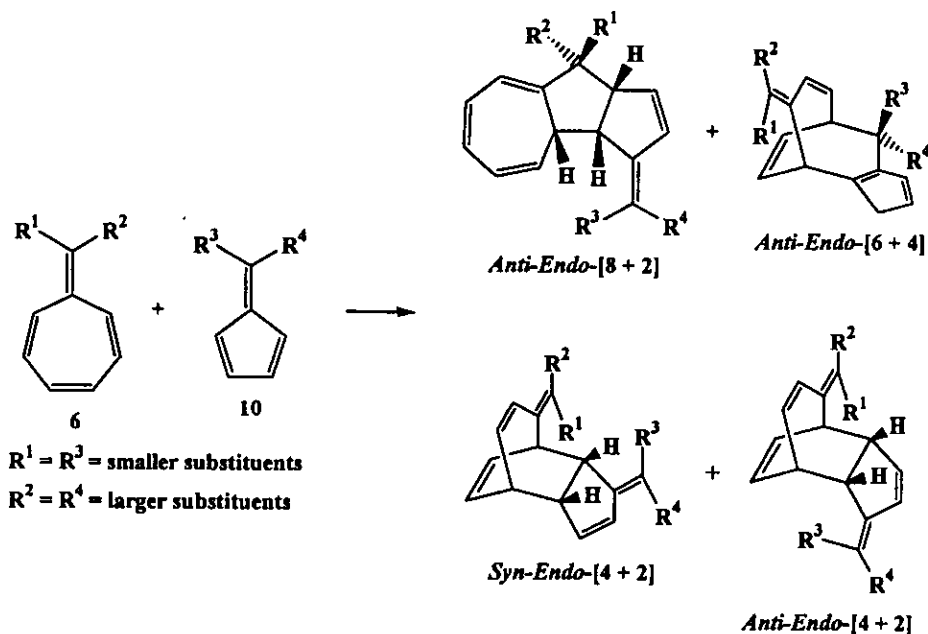
Scheme 2.

1,5-sigmatropic hydrogen shift in the cyclopentadiene moiety.^{6–8,11–15} Additional structural evidence for **20c** is the [4+2] cycloaddition reaction of **20c** with DMAD,^{6,11–14} which gave **21c**, which in turn afforded ketone **22c** (Scheme 4) upon acid hydrolysis.

The IR spectrum of cycloadduct **22c** showed characteristic α,β -unsaturated ketone and ester absorptions at 1660 and 1720 cm^{-1} , respectively. The structure was eventually proved by a complete analysis of its ^1H NMR spectra, including 2D ^1H – ^1H COSY and NOESY techniques (Fig. 2), and comparison of its spectra to those of related compounds.^{6,11–14} The ^1H NMR spectrum showed sharp

singlets at δ 1.11 and 1.32 (Me') for the two methyl groups on the saturated carbon, doublets at δ 1.82 and 2.19 for the methylene group (H-5), triplets for H-10, H-8, and H-9 at δ 2.95, 5.87, and 6.25, respectively, broad multiplets for H-4 and H-7 at δ 3.74 and 3.80, respectively, a doublet for H-12 at δ 5.93, a broad doublet for H-3 at δ 6.61, and a doublet of doublets for H-11 at δ 6.84. The appropriate methyl ester resonances at δ 3.70 and 3.80 were also observed. The NOE correlations in the NOESY spectrum, Me' to H-3, H-10, and H-11 and Me to H-3, H-9, and H-10 as shown in Figure 2, confirmed the stereochemistry for this cycloadduct.

Interestingly, heating a dilute solution of **20c** in refluxing



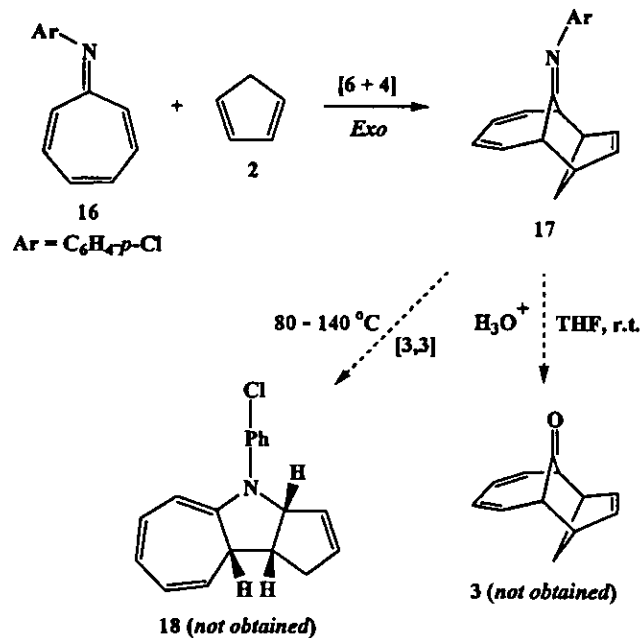
Scheme 3.

xylene mainly led to a retro-[6+4] cycloaddition reaction of **20c** to starting materials **16** and **10c**, along with minor amounts of another [6+4] cycloadduct, **23c**. Cycloadduct **23c** must arise from a 1,5-sigmatropic hydrogen shift in the cyclopentadiene moiety of **20c**. Additional structural evidence for **23c** is the [4+2] cycloaddition reaction of **23c** with DMAD, which gave **24c**, which in turn afforded ketone **25c** (Scheme 5) upon acid hydrolysis. The structure of **25c** was eventually proved by a complete analysis of its ^1H NMR spectra, including 2D ^1H - ^1H COSY and NOESY techniques (Fig. 2), and comparison of its spectra to those of related cycloadduct **22c**. The NOE correlations in the NOESY spectrum, Me' to H-3, H-10, and H-11, Me to H-3,

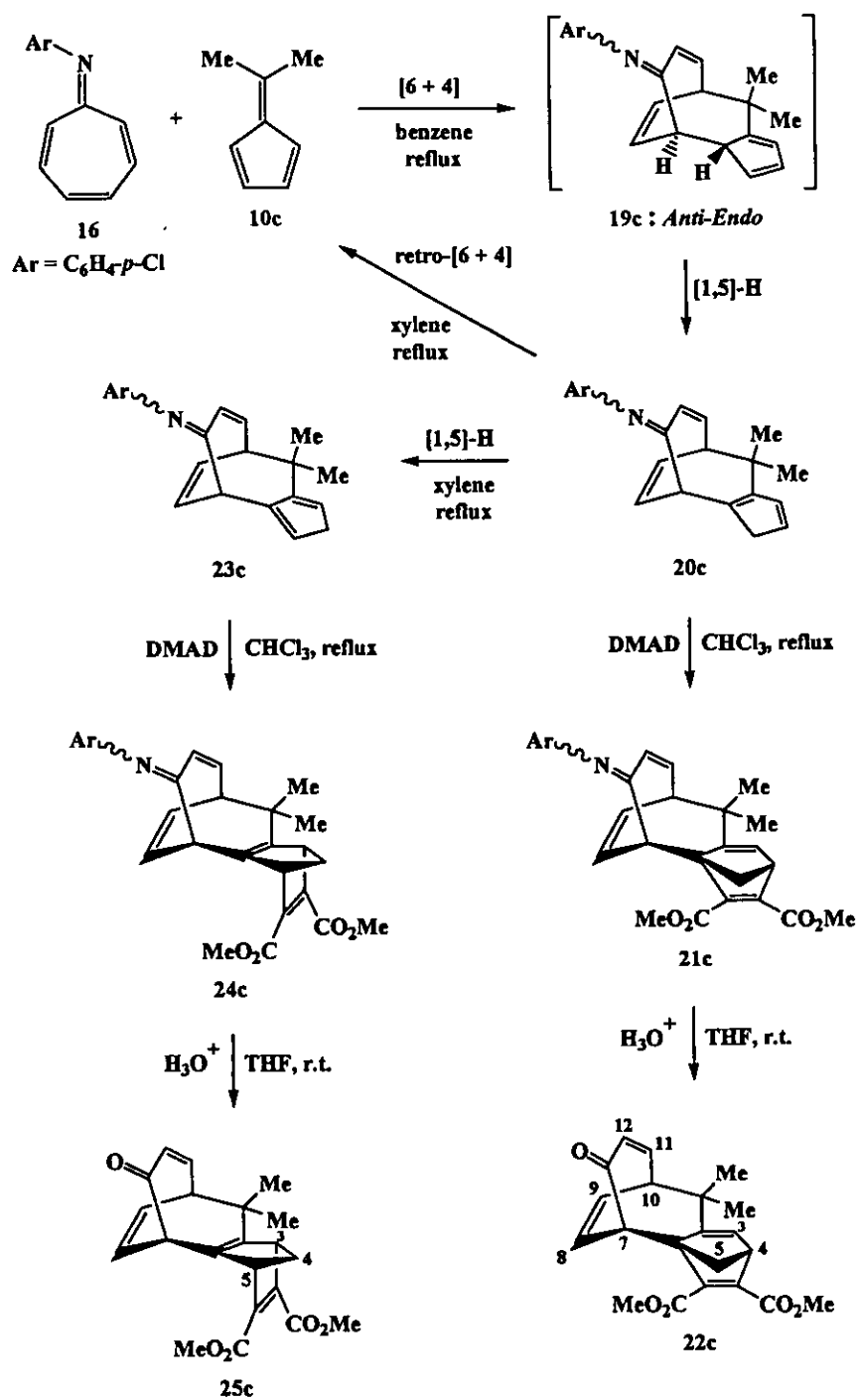
H-9, and H-10, and H-5 to H-7 as shown in Figure 2, confirmed the stereochemistry for this cycloadduct.

When the reaction of **16** and **10c** was carried out in refluxing xylene for 5 h, the *syn-endo*-[4+2] cycloadduct **26c** and *anti-endo*-[6+4] cycloadduct **20c** were obtained in a ratio of 2.4:1 in 60% isolated yield (Scheme 6 and Table 1). A trace of the [6+4] cycloadduct **23c** was also obtained. With longer reaction time (7 h), **26c** was formed as the main product. Additional structural evidence for **26c** is acid hydrolysis of **26c** affords the corresponding ketone **27c**. Traces of the [6+4] cycloadducts **22c/25c** (after DMAD and H_3O^+) were also isolated. The IR spectrum of cycloadduct **27c** showed a characteristic α,β -unsaturated ketone absorption at 1660 cm^{-1} . The structure was eventually proved by a complete analysis of its ^1H NMR spectra, including 2D ^1H - ^1H COSY and NOESY techniques (Fig. 2), and comparison of its spectra to those of related compounds.^{6,11–14} The ^1H NMR spectrum showed sharp singlets at δ 1.73 and 1.78 (Me') for the two methyl groups on the unsaturated carbon, doublets at δ 3.22 and 5.74 for H-1 and H-11, respectively, triplets for H-6, H-7, and H-8 at δ 3.38, 6.22, and 5.97, respectively, doublet of doublets for H-3 and H-12 at δ 6.39 and 7.10, respectively, and broad multiplets for H-4 and H-5/H-9 at δ 5.55 and 3.60, respectively. The small coupling constants between H-1 and H-9 and between H-5 and H-6 are compatible only with an *endo* stereochemistry for this cycloadduct.^{11–18} H-5 was coupled to H-1, H-3, H-4, and H-6, respectively, indicating a *syn* regiochemistry. The NOE correlations in the NOESY spectrum, Me' to H-1 and H-9, Me to H-3, and H-4 to H-6, as shown in Figure 2, further confirmed the stereochemistry for this cycloadduct.

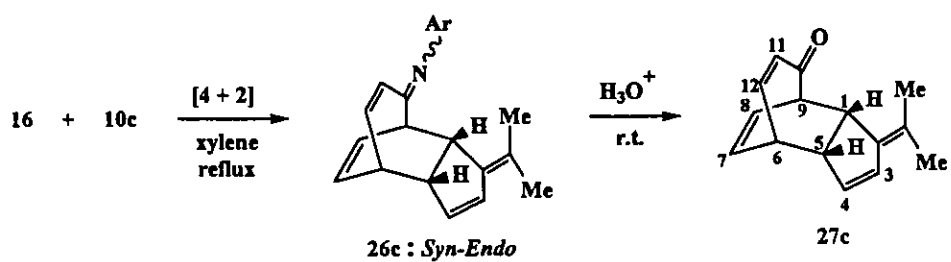
The present results show that the [6+4] cycloadduct **20c**, although formed under mild conditions, mainly reverted back to starting materials **16** and **10c** at higher temperatures and in turn recombined to form the thermodynamically



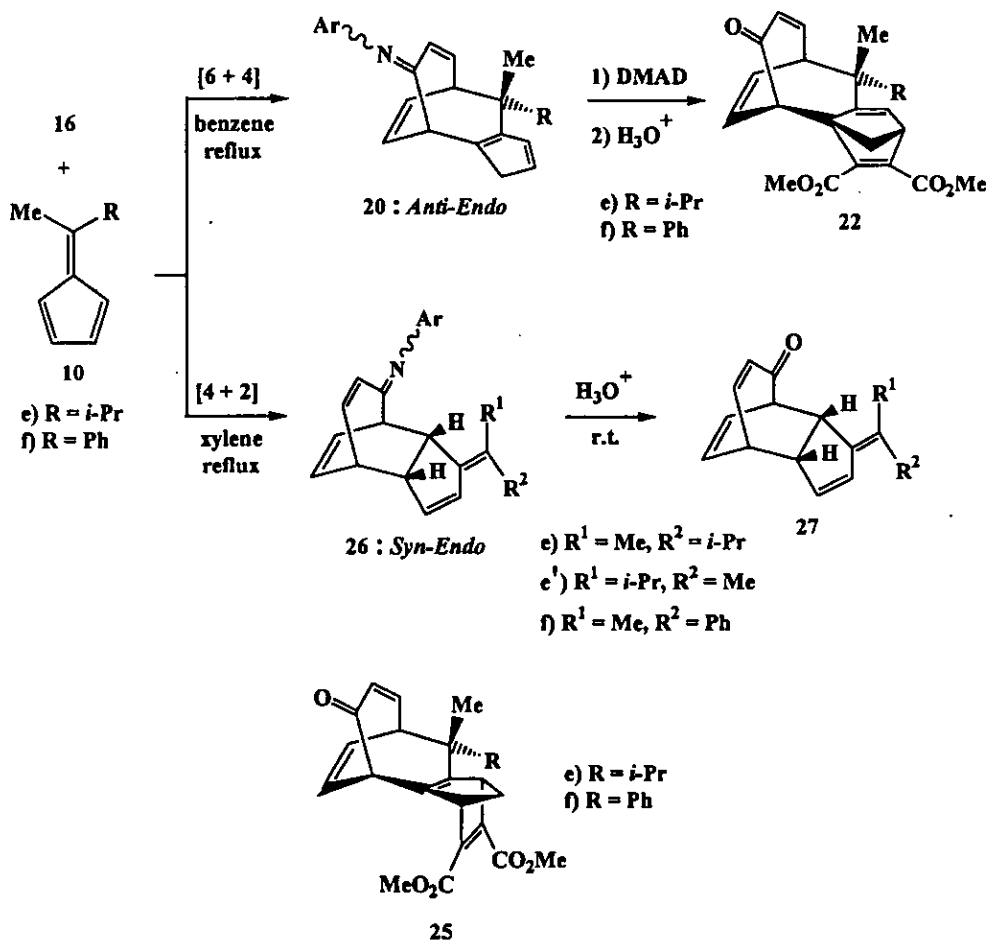
Scheme 4.



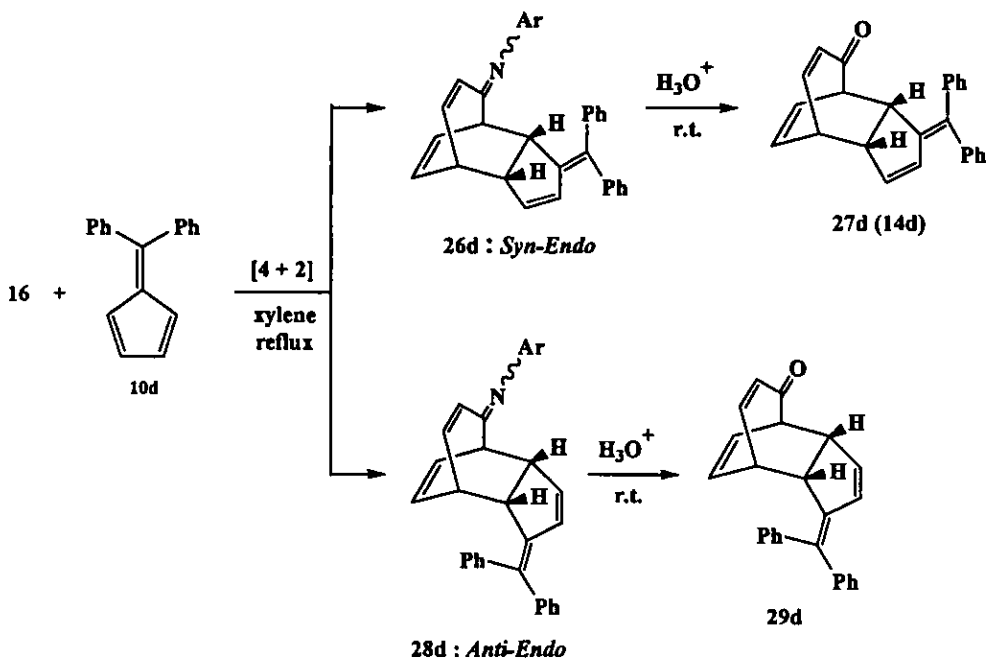
Scheme 5.



Scheme 6.



Scheme 7.



Scheme 8.

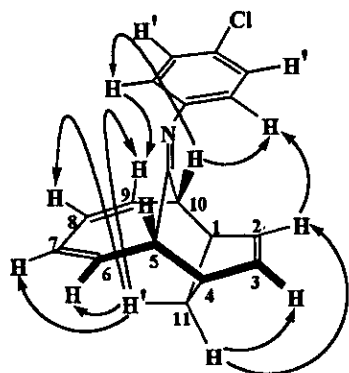


Figure 1. Structure of compound 17 and NOE correlations.

more stable [4+2] cycloadduct **26c**. The [6+4] cycloaddition reactions took place with exclusive *endo* diastereoselectivity and *anti* regioselectivity. However, the [4+2] cycloaddition reactions took place with exclusive *endo* diastereoselectivity and *syn* regioselectivity.

2.3. Reactions of 8-(*p*-chlorophenyl)-8-azaheptafulvene (**16**) with unsymmetrically substituted 6-isopropyl-6-methylfulvene (**10e**) and 6-methyl-6-phenylfulvene (**10f**) and symmetrically substituted 6,6-diphenylfulvene (**10d**) (Schemes 7 and 8)

The reactions of 8-(*p*-chlorophenyl)-8-azaheptafulvene (**16**) with unsymmetrically substituted fulvenes **10e** and **10f** in refluxing benzene afforded only the *anti-endo*-[6+4] cycloadducts **20e** and **20f** in 51 and 45% yields, respectively (Scheme 7 and Table 1). Additional structural evidence for **20e** and **20f** are the [4+2] cycloaddition reactions of **20e** and **20f** with DMAD, which gave **21e** and **21f**, which in turn afforded ketones **22e** and **22f**, respectively upon acid hydrolysis.

When **16** was reacted with fulvene **10e** in refluxing xylene for 5 h, the *syn-endo*-[4+2] cycloadducts **26e** and **26e'** and the *anti-endo*-[6+4] cycloadduct **20e** were obtained in a ratio of 4:1 in 50% isolated yield (Scheme 7 and Table 1). Similarly, **16** reacted with more hindered fulvene **10f** in

Table 1. Cycloaddition reactions of 8-(*p*-chlorophenyl)-8-azaheptafulvene (**16**) with fulvenes **10c–f**

Reactants 16+10x X	Solvent	Temp	Time (h)	Adduct (ratio)	Yield (%)
c	Chloroform	Room temperature	24	20c	10
	Benzene	Reflux	12	20c	56
	Xylene	Reflux	5	26c + 20c (2.4:1)+ 23c (trace)	60
	Xylene	Reflux	7	26c + 20c (trace)+ 23c (trace)	65
e	Benzene	Reflux	5	20e	51
	Xylene	Reflux	5	26e/e' + 20e (4:1)+ 25e (trace)	50
	Xylene	Reflux	7	26e + 26e' (1.4:1) ^a + 20e (trace)+ 25e (trace)	60
f	Benzene	Reflux	5	20f	45
	Xylene	Reflux	3	26f + 20f (3.3:1)+ 25f (trace)	60
	Xylene	Reflux	7	26f + 20f (trace)+ 25f (trace)	62
d	Xylene	Reflux	7	26d + 28d (1:1.5)	48

^a Ratio of adducts was estimated from ¹H NMR data in the inseparable mixture of adducts.

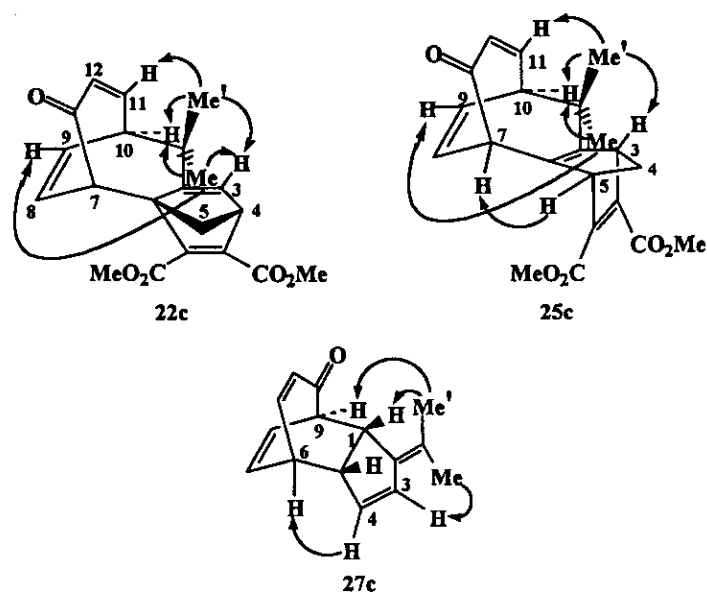


Figure 2. Structure of compound **22c**, **25c**, and **27c** and NOE correlations.

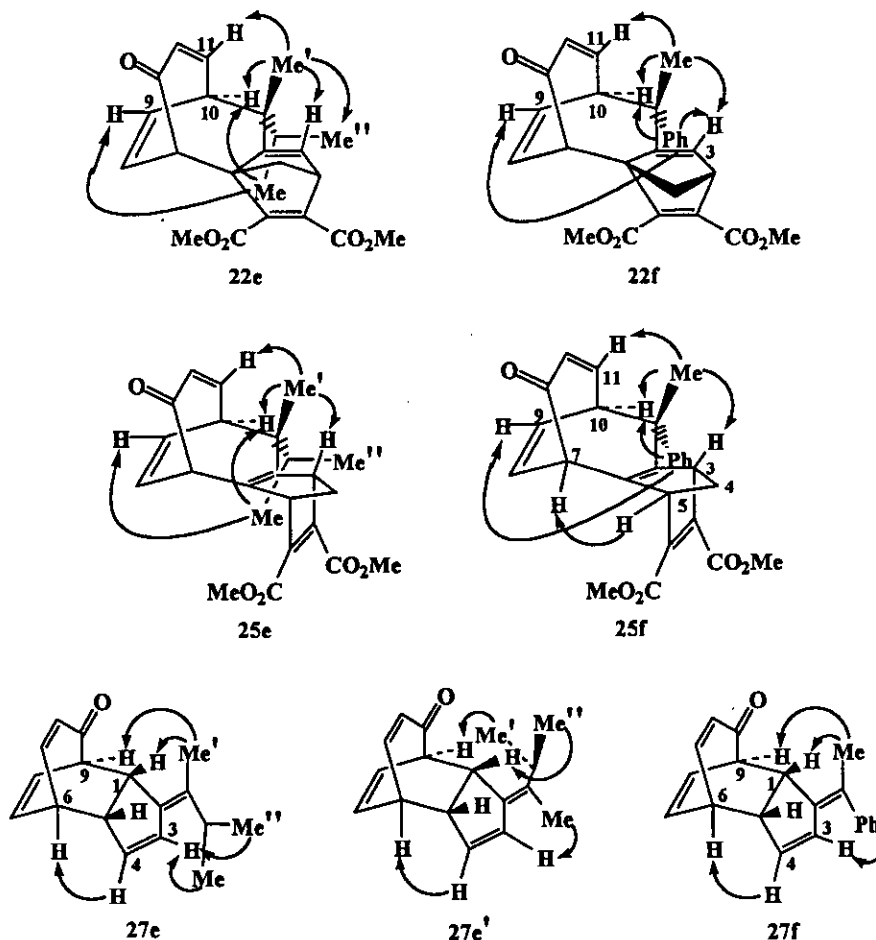


Figure 3. Structure of compound 22e,f, 25e,f, and 27e,e',f and NOE correlations.

refluxing xylene for 5 h, the *syn-endo*-[4+2] cycloadducts **26f** and *anti-endo*-[6+4] cycloadduct **20f** were obtained in a ratio of 3.3:1 in 60% isolated yield (Scheme 7 and Table 1). A trace of the [6+4] cycloadducts **25e/25f** (after DMAD and H₃O⁺) was also isolated. With longer reaction time (7 h), **26e/26e'** (1.4:1 mixture of inseparable regioisomers) and **26f** were formed as the main products in 60 and 62% yields, respectively. Additional structural evidence for **26e**, **26e'**, is that their acid hydrolysis affords the corresponding ketones **27e**, **27e'** and **27f**, respectively.

In contrast to the reactions of **16** and **10c**, **10e**, and **10f**, the reaction of **16** with more hindered 6,6-diphenylfulvene (**10d**) in refluxing xylene afforded the *syn-endo*- (**26d**) and *anti-endo*- (**28d**) [4+2] cycloadducts in a ratio of 1:1.5 in 48% isolated yield (Scheme 8 and Table 1). No [6+4] cycloadduct was observed. Additional structural evidence for **26d** and **28d** is acid hydrolysis of **26d** and **28d** affords the corresponding ketones **14d** and **29d**, respectively. The structure of these cycloadducts were eventually proved by complete analysis of their ¹H NMR spectra, including 2D ¹H–¹H COSY and NOESY techniques (Figs. 3 and 4), and comparison of their spectra to those of related cycloadducts **22c**, **25c**, and **27c**.

Similar to the reaction of **16** and **10c**, these [6+4] cycloaddition reactions took place with exclusive *endo* diastereoselectivity and *anti* regioselectivity. The most

important result of the present work is the finding that the exocyclic substituents of the fulvenes exert great influence on the periselectivity between the two reaction sides. In all cases with the unsymmetrically 6,6-disubstituted fulvenes, **10e** and **10f**, these [6+4] cycloaddition reactions took place exclusively on the side that is *anti* to the larger exocyclic substituent of the fulvenes. This periselectivity can be explained by comparing the various transition states involved in the cycloadditions. The only possible transition-state geometry (*anti-endo*) for these cycloaddition reactions is shown in Figure 5. Careful examination of this

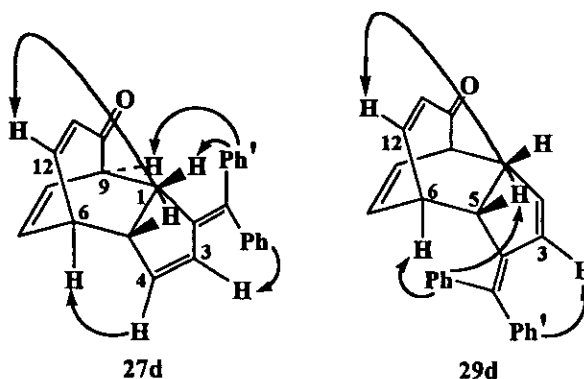


Figure 4. Structure of compound 27d, and 29d, and NOE correlations.

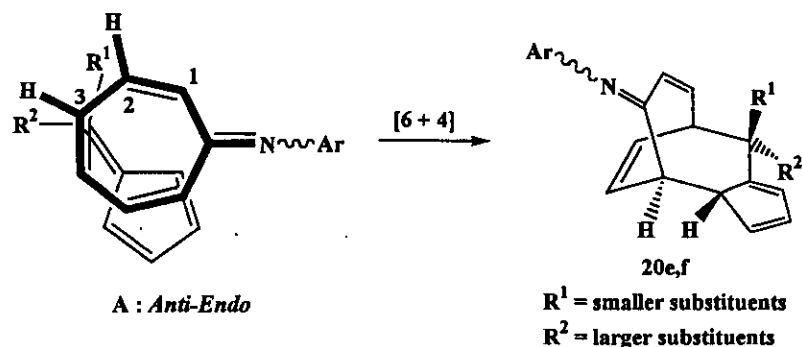


Figure 5. *Anti-endo* transition state, A, of the [6+4] cycloaddition reactions.

transition state suggests that possible steric repulsion mainly results from the proximity of the R¹ group of the fulvene to the C-2 and C-3 methine groups of the 8-azaheptafulvene. Thus, transition state A, with the smaller R¹ substituent is more favorable and leads to the formation of cycloadducts 20e and 20f.

The present results also show that the [4+2] cycloaddition reactions of 16 with 10e and 10f took place preferentially

and exclusively, on the endocyclic double bond that is *anti* to the larger exocyclic substituent of the fulvene. This periselectivity can be explained by comparing the various transition states involved in the cycloadditions. The possible transition-state geometries (*endo*) for these cycloaddition reactions are shown in Figure 6. Examination of these transition states indicates that steric repulsion results from the proximity of the R¹ group of the fulvene to the C-1 methine group of the 8-azaheptafulvene. Thus, transition

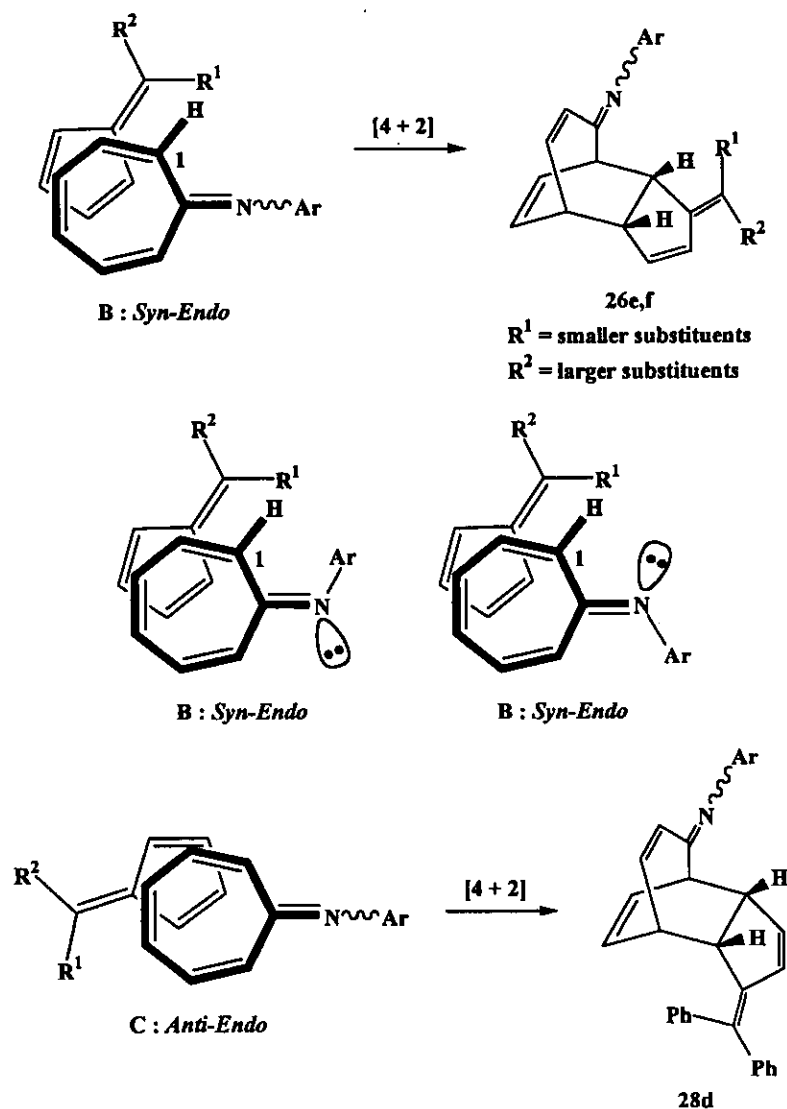


Figure 6. *Endo* transition states of the *syn*-[4+2] (B) and *anti*-[4+2] (C) cycloaddition reactions.

state **B** is more favorable and leads to the formation of cycloadducts **26e**. Increasing steric bulk of the larger one of the two exocyclic substituents on the fulvenes should cause higher periselectivity, and thus the reaction of fulvene **10f** with **16** took place exclusively on the endocyclic double bond that is *anti* to the larger exocyclic substituent of the fulvene to give the cycloadduct **26f**. As Table 1 indicates, the [4+2] cycloaddition reactions of fulvenes **10c**, **10e** and **10f** with **16**, proceed with exclusively *syn* regioselectivity. With a secondary steric repulsion from the proximity of the R¹ group of the fulvene to the exocyclic Ar group and/or nonbonded electron-pairs on the nitrogen of the 8-azaheptafulvene in transition state **B**, a nonbonded interaction which is absent in **C**, fulvene **10d**, with two bulky exocyclic substituents, that destabilize the *syn* transition state **B**, reacted with **16** preferentially to give the *anti*-[4+2] cycloadduct **28d**.

All these results show that the exocyclic substituent effects exert controlling influence upon the periselectivity and regioselectivity of these cycloadditions.

3. Experimental

3.1. General

¹H NMR spectra were determined on either a Varian Mercury-200 or a Bruker DMX-500 spectrometer and chemical shifts are reported as δ values in ppm relative to TMS ($\delta=0.00$) as the internal standard and CDCl₃ as the solvent. Infrared (IR) spectra were determined on a Perkin-Elmer 1600 FT-IR spectrometer. Mass spectra were determined on a VG Platform Electrospray mass spectrometer. High resolution mass spectra (HRMS) were determined on a FINNIGAN MAT 95S mass spectrometer. All reagents were of reagent grade and were purified prior to use. All reactions were performed under an inert atmosphere of nitrogen. The preparations of 8-(*p*-chlorophenyl)-8-azaheptafulvene (**16**)¹⁹ and fulvenes **10c–f**^{20,21} were by literature procedures.

3.2. Cycloaddition reactions of 8-(*p*-chlorophenyl)-8-azaheptafulvene (**16**) with cyclopentadiene (**2**)

A solution of 8-(*p*-chlorophenyl)-8-azaheptafulvene (**16**) (215 mg, 1.00 mmol) in 25 mL of freshly distilled cyclopentadiene (**2**) was stirred at room temperature for 24 h afforded a yellow oil. Purification by silica gel flash chromatography, using 5% EtOAc in *n*-hexane as eluant, gave **17** (98 mg, 35%) as a yellowish oil: ¹H NMR δ 1.37–1.42 (m, 1H, H-11), 2.10 (d, 1H, *J*=11.2 Hz, Me), 2.81–2.83 (m, 1H, H-1), 2.98–2.99 (m, 1H, H-4), 3.25–3.28 (m, 1H, H-10), 3.34–3.37 (m, 1H, H-5), 5.56 (bdd, 1H, *J*=7.4, 11.5 Hz, H-9), 5.81 (dd, 1H, *J*=2.5, 5.6 Hz, H-2), 5.94 (bdd, 1H, *J*=7.4, 11.5 Hz, H-6), 5.98–6.02 (m, 2H, H-7-8), 6.05 (dd, 1H, *J*=2.5, 5.6 Hz, H-3), 6.50 (d, 2H, *J*=8.5 Hz, Ph), 7.15 (d, 2H, *J*=8.6 Hz, Ph); ν_{\max} (KBr): 2940, 1659, 1587, 1483, 1340, 1192 cm⁻¹; MS *m/z* 281 (M⁺); HRMS: calcd for C₁₈H₁₆ClN: 281.0972; found: 281.0983.

3.3. Attempted hydrolysis of cycloadduct **17**

A solution of **17** (20 mg) in 10 mL of THF, 5 mL of water, and 3 mL of 37% HCl was vigorously stirred at room temperature for 24 h. The mixture was concentrated in vacuo and extracted with Et₂O. The combined organic extracts were washed with saturated aqueous NaHCO₃ and brine, dried over anhydrous MgSO₄, filtered, and concentrated in vacuo. Purification by silica gel flash chromatography, using 5% EtOAc in *n*-hexane as eluant, gave mainly the starting material **17**. No hydrolyzed cycloadduct **3** was obtained.

3.4. Attempted thermolysis of [6+4] cycloadduct **17**

The attempted thermolysis of **17** (20 mg) in 30 mL of refluxing benzene or xylene for 24 h did not proceed; mainly the starting material **17** was recovered. No [3,3] sigmatropic rearranged [8+2] cycloadduct **18** was obtained.

3.5. General procedure for cycloaddition reactions of 8-(*p*-chlorophenyl)-8-azaheptafulvene (**16**) with fulvenes **2c–f**

A solution containing 1.0 mmol of 8-(*p*-chlorophenyl)-8-azaheptafulvene (**16**) and 1.1 mmol of fulvenes **10c–f** in 6 mL of solvent was stirred (the solvents and the reaction conditions are all indicated in Table 1). After evaporation of the excess solvent under reduced pressure, the crude mixture was subjected to silica gel flash chromatography with 5–15% EtOAc in *n*-hexane as the eluant to give a complex mixture. A solution of this complex mixture and excess DMAD in 6 mL of chloroform was stirred under reflux for 7 h to afford a yellow oil. Column chromatography, using 20% EtOAc in *n*-hexane as eluant to give the [6+4] cycloadducts **21** and **24** and the [4+2] cycloadducts **26** and **28**. Then, same procedure as in **17**, acid hydrolysis to give the corresponding ketone **22**, **25**, **27**, and **29**, respectively. IR spectra data for cycloadducts (cm⁻¹): 1720–1725 (O=CROME); 1655–1665 (O=CRR'). Other data, ¹H NMR, MS; HRMS for:

3.5.1. Compound 22c. ¹H NMR δ 1.11 (s, 3H, Me'), 1.32 (s, 3H, Me), 1.82 (d, 1H, *J*=6.6 Hz, H-5), 2.19 (d, 1H, *J*=6.6 Hz, H-5), 2.95 (t, 1H, *J*=8.5 Hz, H-10), 3.70 (s, 3H, -CO₂Me), 3.73–3.75 (m, 1H, H-4), 3.78–3.81 (m, 4H, H-7, -CO₂Me), 5.87 (t, 1H, *J*=9.1 Hz, H-8), 5.93 (d, 1H, *J*=11.8 Hz, H-12), 6.25 (bt, 1H, *J*=9.5 Hz, H-9), 6.61 (bd, 1H, *J*=3.4 Hz, H-3), 6.84 (dd, 1H, *J*=11.8, 8.5 Hz, H-11); MS *m/z* 354 (M⁺); HRMS: calcd for C₂₁H₂₂O₅: 354.1467; found: 354.1453.

3.5.2. Compound 25c. ¹H NMR δ 1.04 (s, 3H, Me'), 1.32 (s, 3H, Me), 2.05 (bd, 1H, *J*=6.7 Hz, H-4), 2.16 (bd, 1H, *J*=6.7 Hz, H-4), 2.99 (t, 1H, *J*=8.3 Hz, H-10), 3.62 (bs, 1H, H-5), 3.72 (s, 3H, -CO₂Me), 3.74 (s, 3H, -CO₂Me), 3.87 (bd, 1H, *J*=8.3 Hz, H-7), 3.89 (bs, 1H, H-3), 5.74 (d, 1H, *J*=11.9 Hz, H-12), 6.09 (t, 1H, *J*=8.3 Hz, H-8), 6.22 (bt, 1H, *J*=8.3 Hz, H-9), 6.53 (dd, 1H, *J*=8.3, 11.9 Hz, H-11); MS *m/z* 354 (M⁺); HRMS: calcd for C₂₁H₂₂O₅: 354.1467; found: 354.1457.

3.5.3. Compound 27c. ¹H NMR δ 1.73 (s, 3H, Me), 1.78 (s,

3H, Me'), 3.22 (bd, 1H, $J=7.5$ Hz, H-1), 3.38 (bt, 1H, $J=7.8$ Hz, H-6), 3.59–3.61 (m, 2H, H-5, H-9), 5.54–5.56 (m, 1H, H-4), 5.74 (d, 1H, $J=10.9$ Hz, H-11), 5.97 (t, 1H, $J=7.8$ Hz, H-8), 6.22 (t, 1H, $J=7.8$ Hz, H-7), 6.39 (dd, 1H, $J=2.1, 5.7$ Hz, H-3), 7.10 (dd, 1H, $J=8.7, 10.9$ Hz, H-12); MS m/z 212 (M^+); HRMS: calcd for $C_{15}H_{16}O$: 212.1201; found: 212.1195.

3.5.4. Compound 22e. 1H NMR δ 0.49 (d, 3H, $J=6.8$ Hz, $-CHMeMe''$), 0.86 (d, 3H, $J=6.8$ Hz, $-CHMeMe''$), 1.07 (s, 3H, Me'), 1.83 (d, 1H, $J=6.7$ Hz, H-5), 1.86–1.93 (m, 1H, $-CHMeMe''$), 2.16 (d, 1H, $J=6.7$ Hz, H-5), 3.19 (t, 1H, $J=8.3$ Hz, H-10), 3.70 (s, 3H, $-CO_2Me$), 3.74–3.77 (m, 4H, H-7, $-CO_2Me$), 5.88 (t, 1H, $J=8.7$ Hz, H-8), 5.93 (d, 1H, $J=11.9$ Hz, H-12), 6.24 (bt, 1H, $J=8.7$ Hz, H-9), 6.49 (bs, 1H, H-3), 6.81 (dd, 1H, $J=8.5, 11.9$ Hz, H-11); MS m/z 382 (M^+); HRMS: calcd for $C_{23}H_{26}O_5$: 382.1780; found: 382.1771.

3.5.5. Compound 25e. 1H NMR δ 0.92 (s, 3H, Me'), 0.95 (d, 3H, $J=6.9$ Hz, $-CHMeMe''$), 1.02 (d, 3H, $J=6.9$ Hz, $-CHMeMe''$), 2.10–2.15 (m, 3H, H-4, $-CHMeMe''$), 3.19 (t, 1H, $J=8.3$ Hz, H-10), 3.62 (bs, 1H, H-5), 3.72 (s, 3H, $-CO_2Me$), 3.73 (s, 3H, $-CO_2Me$), 3.85–3.88 (m, 2H, H-3, H-7), 5.68 (d, 1H, $J=11.9$ Hz, H-12), 6.03 (t, 1H, $J=8.9$ Hz, H-8), 6.17 (t, 1H, $J=9.1$ Hz, H-9), 6.43 (dd, 1H, $J=8.5, 11.9$ Hz, H-11); MS m/z 382 (M^+); HRMS: calcd for $C_{23}H_{26}O_5$: 382.1780; found: 382.1765.

3.5.6. Compound 27e. 1H NMR δ 0.92–0.98 (m, 6H, $-CHMeMe''$), 1.67 (s, 3H, Me'), 2.79–2.85 (m, 1H, $-CHMeMe''$), 3.19 (bd, 1H, $J=7.5$ Hz, H-1), 3.37 (bt, 1H, $J=7.8$ Hz, H-6), 3.56–3.58 (m, 2H, H-5, H-9), 5.52–5.54 (m, 1H, H-4), 5.76 (d, 1H, $J=10.9$ Hz, H-11), 5.95–6.01 (m, 1H, H-8), 6.21 (t, 1H, $J=7.8$ Hz, H-7), 6.46 (dd, 1H, $J=2.0, 5.7$ Hz, H-3), 7.10 (dd, 1H, $J=8.7, 10.9$ Hz, H-12); MS m/z 240 (M^+); HRMS: calcd for $C_{17}H_{20}O$: 240.1514; found: 240.1504.

3.5.7. Compound 27e'. 1H NMR δ 0.92–0.98 (m, 3H, $-CHMeMe''$), 1.07 (d, 3H, $J=6.8$ Hz, $-CHMeMe''$), 1.61 (s, 3H, Me), 2.71–2.77 (m, 1H, $-CHMeMe''$), 3.25 (bd, 1H, $J=7.5$ Hz, H-1), 3.37 (bt, 1H, $J=7.8$ Hz, H-6), 3.56–3.58 (m, 2H, H-5), 3.50 (d, 1H, $J=7.4$ Hz, H-9), 5.55–5.57 (m, 1H, H-4), 5.76 (d, 1H, $J=10.9$ Hz, H-11), 5.95–6.01 (m, 1H, H-8), 6.21 (t, 1H, $J=7.8$ Hz, H-7), 6.38 (dd, 1H, $J=2.1, 5.7$ Hz, H-3), 7.10 (dd, 1H, $J=8.7, 10.9$ Hz, H-12); MS m/z 240 (M^+); HRMS: calcd for $C_{17}H_{20}O$: 240.1514; found: 240.1504.

3.5.8. Compound 22f. 1H NMR δ 1.59 (s, 3H, Me), 2.01 (d, 1H, $J=6.8$ Hz, H-5), 2.31 (d, 1H, $J=6.8$ Hz, H-5), 3.56 (s, 3H, $-CO_2Me$), 3.79 (m, 3H, $-CO_2Me$), 3.81–3.85 (m, 2H, H-4, H-10), 3.92 (d, 1H, $J=8.3$ Hz, H-7), 5.68 (t, 1H, $J=9.5$ Hz, H-8), 5.87 (bt, 1H, $J=9.5$ Hz, H-9), 6.04 (d, 1H, $J=11.5$ Hz, H-12), 6.86 (bd, 1H, $J=2.8$ Hz, H-3), 6.96 (dd, 1H, $J=8.5, 11.5$ Hz, H-11), 7.04–7.06 (m, 2H, Ph), 7.11–7.13 (m, 1H, Ph), 7.15–7.18 (m, 2H, Ph); MS m/z 416 (M^+); HRMS: calcd for $C_{26}H_{24}O_5$: 416.1624; found: 416.1629.

3.5.9. Compound 25f. 1H NMR δ 1.40 (s, 3H, Me), 2.22 (bd, 1H, $J=6.9$ Hz, H-4), 2.36 (bd, 1H, $J=6.9$ Hz, H-4), 3.30 (t, 1H, $J=8.6$ Hz, H-10), 3.70 (bs, 4H, H-3, $-CO_2Me$),

3.76 (bs, 4H, H-5, $-CO_2Me$), 3.98 (bd, 1H, $J=8.3$ Hz, H-7), 5.64 (t, 1H, $J=8.2$ Hz, H-9), 5.81 (d, 1H, $J=11.9$ Hz, H-12), 6.02 (t, 1H, $J=8.3$ Hz, H-8), 6.61 (dd, 1H, $J=8.5, 11.9$ Hz, H-11), 7.21–7.22 (m, 1H, Ph), 7.28–7.31 (m, 2H, Ph), 7.37–7.39 (m, 2H, Ph); MS m/z 416 (M^+); HRMS: calcd for $C_{26}H_{24}O_5$: 416.1624; found: 416.1629.

3.5.10. Compound 27f. 1H NMR δ 2.14 (s, 3H, Me), 3.37–3.41 (m, 2H, H-1, H-6), 3.64 (bd, 1H, $J=7.1$ Hz, H-5), 3.76 (bd, 1H, $J=7.4$ Hz, H-9), 5.58–5.59 (m, 1H, H-4), 5.80 (d, 1H, $J=11.0$ Hz, H-11), 6.04 (t, 1H, $J=7.4$ Hz, H-8), 6.24–6.27 (m, 2H, H-3, H-7), 7.10 (dd, 1H, $J=8.6, 11.0$ Hz, H-12), 7.13–7.17 (m, 3H, Ph), 7.26–7.30 (m, 2H, Ph); MS m/z 274 (M^+); HRMS: calcd for $C_{20}H_{18}O$: 274.1358; found: 274.1351.

3.5.11. Compound 27d. 1H NMR δ 3.26–3.31 (m, 2H, H-6, H-9), 3.60–3.63 (m, 1H, H-5), 3.80 (bd, 1H, $J=7.1$ Hz, H-1), 5.64 (bd, 1H, $J=10.9$ Hz, H-11), 5.81 (dd, 1H, $J=2.4, 5.7$ Hz, H-4), 5.96 (t, 1H, $J=7.9$ Hz, H-8), 6.27 (t, 1H, $J=7.9$ Hz, H-7), 6.38 (dd, 1H, $J=2.4, 5.7$ Hz, H-3), 7.04 (dd, 1H, $J=8.7, 10.9$ Hz, H-12); 7.07–7.18 (m, 5H, Ph), 7.18–7.34 (m, 5H, Ph'); MS m/z 336 (M^+); HRMS: calcd for $C_{25}H_{20}O$: 336.1514; found: 336.1502.

3.5.12. Compound 29d. 1H NMR δ 3.02 (t, 1H, $J=7.9$ Hz, H-6), 3.45–3.48 (m, 2H, H-1, H-9), 3.62 (bd, 1H, $J=7.4$ Hz, H-5), 5.66 (dd, 1H, $J=11.0$ Hz, H-11), 5.91 (dd, 1H, $J=2.5, 5.6$ Hz, H-2), 5.98 (t, 1H, $J=7.9$ Hz, H-8), 6.27 (t, 1H, $J=7.9$ Hz, H-7), 6.34 (dd, 1H, $J=1.6, 5.6$ Hz, H-3), 6.70 (dd, 1H, $J=7.9, 11.0$ Hz, H-12); 7.09–7.25 (m, 5H, Ph'), 7.25–7.40 (m, 5H, Ph); MS m/z 336 (M^+); HRMS: calcd for $C_{25}H_{20}O$: 336.1514; found: 336.1501.

Acknowledgements

We are grateful to the National Science Council of the Republic of China for financial support of this research.

References

1. Cookson, R. C.; Drake, B. V.; Hudec, J.; Morrison, A. *J. Chem. Soc., Chem. Commun.* **1966**, 15.
2. Ito, S.; Fujise, Y.; Okuda, T.; Inoue, Y. *Bull. Chem. Soc. Jpn* **1966**, *39*, 1351.
3. Machiguchi, T.; Hasegawa, T.; Otani, H.; Ishii, Y. *J. Chem. Soc., Chem. Commun.* **1987**, 1375.
4. Machiguchi, T.; Hasegawa, T.; Ishii, Y.; Yamabe, S.; Minato, T. *J. Am. Chem. Soc.* **1993**, *115*, 11536.
5. Kitahara, Y.; Oda, M. In *Jerusalem Symposia on Quantum Chemistry and Biochemistry. Aromaticity, Pseudo-Aromaticity, Antiaromaticity*; Bergman, D., Pullman, B., Eds.; Academic: New York, 1971; Vol. 3, p 284.
6. Houk, K. N.; Luskus, L. J.; Bhacca, N. S. *J. Am. Chem. Soc.* **1970**, *92*, 6392.
7. Bhacca, N. S.; Luskus, L. J.; Houk, K. N. *Chem. Commun.* **1971**, 109.
8. Houk, K. N.; Luskus, L. J.; Bhacca, N. S. *Tetrahedron Lett.* **1972**, *22*, 2297.

9. Sasaki, T.; Kanematsu, K.; Kataoka, T. *Chem. Lett.* **1973**, 1183.
10. Machiguchi, T.; Hasegawa, T.; Ishii, Y.; Yamabe, S.; Minato, T. *J. Am. Chem. Soc.* **1993**, *115*, 11536.
11. Liu, C.-Y.; Ding, S.-T. *J. Org. Chem.* **1992**, *57*, 4539.
12. Liu, C.-Y.; Ding, S.-T.; Chen, S.-Y.; You, C.-Y.; Shie, H.-Y. *J. Org. Chem.* **1993**, *58*, 1628.
13. Liu, C.-Y.; Shie, H.-Y.; Chen, S.-Y.; You, C.-Y.; Wang, W.-C.; Hua, L.-N.; Yang, H.-J.; Tseng, C.-M. *Tetrahedron* **1997**, *51*, 17275.
14. Liu, C.-Y.; Shie, H.-Y.; Yu, C.-L. *Tetrahedron* **1999**, *55*, 9171.
15. Tegmo-Larsson, I.-M.; Houk, K. N. *Tetrahedron Lett.* **1978**, 941.
16. Ito, S.; Sakan, K.; Fujise, Y. *Tetrahedron Lett.* **1969**, 775.
17. Ito, S.; Takeshita, H.; Shoji, Y. *Tetrahedron Lett.* **1969**, 1815.
18. Ito, S.; Sakan, K.; Fujise, Y. *Tetrahedron Lett.* **1970**, 2873.
19. Sanechika, K.; Kajigaeshi, S.; Kanemasa, S. *Synthesis* **1977**, 202.
20. Stone, K. J.; Little, R. D. *J. Org. Chem.* **1984**, *49*, 1849.
21. Erickson, M. S.; Cornan, J. M.; Garcia, J. G.; McLaughlin, M. L. *J. Org. Chem.* **1992**, *57*, 2504.