

## Can $\pi 6 + \pi 4 = 10$ ? Exploring Cycloaddition Routes to Highly Unsaturated 10-Membered Rings

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**Abstract:** This paper uses DFT and G3(MP2) calculations to examine whether unbridged 10-membered rings can be made by  $\pi 6 + \pi 4$  cycloadditions to (*Z*)- and (*E*)-hexatrienes, hexa-1,5-dien-3-yne, (*Z*)-hexa-1,3-dien-5-yne, hexa-1,2,3,5-tetraenes, and (*Z*)-hexa-3-ene-1,5-diyne. Cycloadditions to four  $4\pi$  reactants, buta-1,3-diene, butenyne, butatriene, and butadiyne, are explored. Thirty different basic cycloadditions are identified, and all are shown to be exothermic according to G3(MP2) calculations; strain energies in the products are comparable with that of cyclodecane itself, despite the presence of *trans*-alkene, alkyne, allene, cumulene, and *s-trans* diene moieties. The major obstacles to the isolation of  $6 + 4$  cycloaddition products are competing  $\pi 4 + \pi 2$  cycloadditions and, especially, rapid Cope rearrangement of the products, but, in many cases, the judicious introduction of substituents can overcome these problems so that practical syntheses should be possible. Reactions between (*E*)-hexa-1,3,5-triene and *s-trans*-buta-1,3-diene are shown to have substantially lower activation energies than those involving (*Z*)-hexa-1,3,5-triene reacting with either *s-cis*- or *s-trans*-buta-1,3-diene. Conformationally locked derivatives of *s-cis,s-cis* (*E*)-hexa-1,3,5-trienes can lead to derivatives of (*Z,Z,E*)-cyclodeca-1,3,7-triene that are stable to Cope rearrangement, and reactions should proceed at close to ambient temperatures with suitable activating groups. We predict that it should be possible to prepare suitably substituted derivatives of at least 11 more highly unsaturated ring systems: (5*Z*,7*Z*)-cyclodeca-1,2,5,7-tetraene, (1*Z*,3*Z*)-cyclodeca-1,3-dien-7-yne, (2*Z*,7*E*)-cyclodeca-1,2,3,7-tetraene, (*Z*)-cyclodeca-1,2,3-trien-7-yne, (4*Z*,8*E*)-cyclodeca-1,2,4,8-tetraene, (*Z*)-cyclodeca-1,2,4,5,7-pentaene, (*Z*)-cyclodeca-1,2,4-trien-8-yne, (1*Z*,7*E*)-cyclodeca-1,7-dien-3-yne, (*R,S,E*)-cyclodeca-1,2,4,5,8-pentaene, cyclodeca-1,2,4,5,8,9-hexaene, and (*R,S*)-cyclodeca-1,2,4,5-tetraen-8-yne. In three other cases, we predict that cycloaddition will be followed by unusual and intriguing rearrangements. Cycloadditions can be accelerated by the presence of electron-withdrawing groups in either the  $6\pi$  or  $4\pi$  reactants. Transannular cyclizations of some products may lead to interesting stereocontrolled routes to 6,6- and/or 5,7-bicyclic structures.

Can 10-membered rings be made by  $\pi 6 + \pi 4$  (or simply  $6 + 4$ ) cycloaddition? All known examples of  $6 + 4$  cycloaddition yield bridged-ring products,<sup>1–16</sup> and we are aware of only

one theoretical study<sup>10</sup> and no practical results concerning the preparation of cyclodecane derivatives. It seems that the chemical community has concluded that the formation of unbridged 10-membered rings is not possible; this paper aims to show that this is not the case. It is well-known that the basic  $\pi 4 + \pi 2$  ( $4 + 2$ ) cycloadditions of butadiene with ethene and ethyne suffer from poor yields and are never used preparatively, yet  $4 + 2$  cycloadditions between substituted versions of these reactants are immensely important in synthetic chemistry. We will show that, while all the basic  $6 + 4$  cycloadditions suffer from major problems, the introduction of substituents at appropriate positions can not only lead to lower activation energies for  $6 + 4$  cycloadditions but also overcome competition from  $4 + 2$  cycloadditions and destructive Cope rearrangements,

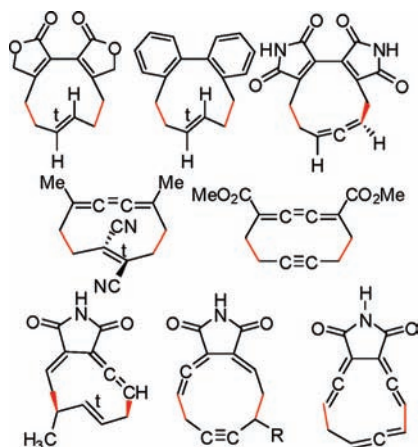
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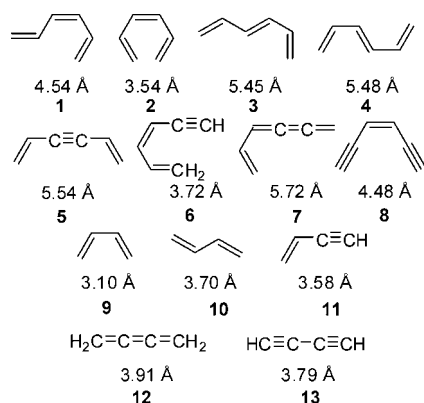
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**Scheme 1.** Selection of 6 + 4 Cycloadducts Whose Formation May Be Practical<sup>a</sup>



<sup>a</sup>  $\sigma$ -bonds formed in the cycloaddition are shown in red.



**Figure 1.** 6 $\pi$  reactants: (*Z*)- and (*E*)-hexatriene in conformations **1**–**4**, hexa-1,5-dien-3-yne (**5**), (*Z*)-hexa-1,3-dien-5-yne (**6**), hexa-1,2,3,5-tetraene (**7**), and (*Z*)-hexa-3-ene-1,5-diyne (**8**). 4 $\pi$  reactants: **9**–**13**. Computed (B3LYP/6-31G\*) distances between terminal carbon atoms are shown.

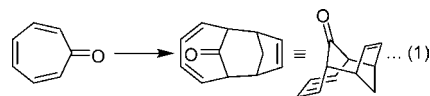
so that formation of a range of unusual cyclodecane derivatives should be practical (see Scheme 1 for examples). These 6 + 4 cycloaddition products possess structural and stereochemical features that would be hard to introduce by any other means, e.g., cyclic *trans* alkenes, *s-trans* cyclic dienes, alkynes, allenes, and cumulenes. Products containing cyclic allenes and cumulenes are likely to be quite reactive, of course, but this may be a potential advantage since further stereocontrolled cyclizations may be possible, leading to interesting bicyclo[4.4.0]- and bicyclo[5.3.0]decane derivatives.

In this paper, we examine reactions between the 6 $\pi$  and 4 $\pi$  components shown in Figure 1, using DFT and G3(MP2) calculations. When stereo- and regiochemical alternatives are included, 30 possible basic 6 + 4 cycloadducts are possible, and formation of almost all of these is predicted by the usually reliable G3(MP2) method to be energetically favorable. It also emerges that the unsaturated 10-membered rings formed in these reactions frequently have lower strain energies than cyclodecane itself. Strain in the products is therefore not a major problem, and in many cases entropies of activation are also not much higher than for 4 + 2 cycloadditions. The real limiting factors in achieving useful 6 + 4 cycloadditions are associated with competition from 4 + 2 cycloadditions and destructive Cope rearrangements. *In particular, rapid Cope rearrangement of*

*initial 6 + 4 adducts frequently means that these would never accumulate in the product.*

## Discussion

The 1965 orbital symmetry rules<sup>17</sup> suggested that 6 + 4 cycloadditions should be possible, and this was confirmed within a year by Cookson and co-workers,<sup>18</sup> who showed that cyclopentadiene and tropone would combine to yield a novel tricyclic ring system:<sup>19–21</sup>



In the 40 years since then, however, while there have been extensive developments of reactions related to eq 1, including metal-promoted process,<sup>1–14</sup> no one has ever made unbridged cyclodecane derivatives by 6 + 4 cycloaddition. A number of factors might work against these reactions:

1. Strain in the products, resulting in unfavorable energetics.
2. Unfavorable entropies of activation.
3. Competition from 4 + 2 cycloadditions.

4. [3,3]-Sigmatropic shifts (Cope rearrangements) of the products, leading to cyclohexane derivatives. As we will see, it is factors 3 and 4 that are the major obstacles to practical 6 + 4 cycloadditions.

In choosing reactants, one simple but important consideration is the difference in the distances between the terminal carbon atoms of the 6 $\pi$  and 4 $\pi$  components (see Figure 1 above), since concerted cycloaddition requires reasonable overlap between the terminal  $\pi$ -orbitals of both components. The Diels–Alder reaction between ethene (1.33 Å) and *s-cis*-butadiene (3.10 Å) shows a difference in length ( $\Delta d$ ) of 1.76 Å, and we assumed that values of  $\Delta d$  up to  $\sim 2$  Å might be acceptable.

It can be seen that cycloadditions to *s-cis*-butadiene (**9**) may be problematic for all but the *s-trans,s-cis* **1** and *s-cis,s-cis* **2** conformations of (*Z*)-hexatriene (and these reactions will suffer from other problems). For other conformations of hexatrienes, the *s-trans* conformer of butadiene (**10**) will be preferred. Note that cycloaddition to a reactant in an *s-trans* conformation necessarily yields a product containing a *trans* double bond. The remaining 4 $\pi$  components **11**–**13** are actually about the same length as **10**. The *s-trans,s-trans* conformations of (*Z*)- and (*E*)-hexatriene are too long (5.79 and 6.11 Å, respectively) to offer good overlap with any of the 4 $\pi$  components, and we could find no good reactions from either of these conformations. Nevertheless, (*E*)-hexatriene conformations **3** and **4** emerge as better 6 $\pi$  components than any conformations of the (*Z*)-isomer; note that products derived from the (*E*)-isomer necessarily possess an *s-trans* diene unit.

Scheme 2 summarizes the 30 fundamental 6 + 4 cycloadditions arising from the reactants in Figure 1. We have investigated all of these, all competing 4 + 2 reactions, subsequent Cope rearrangements, etc. *None of them are likely to be practical in the absence of substituents*, but we show that *all the cases shaded blue* should be practical with appropriate substituents.

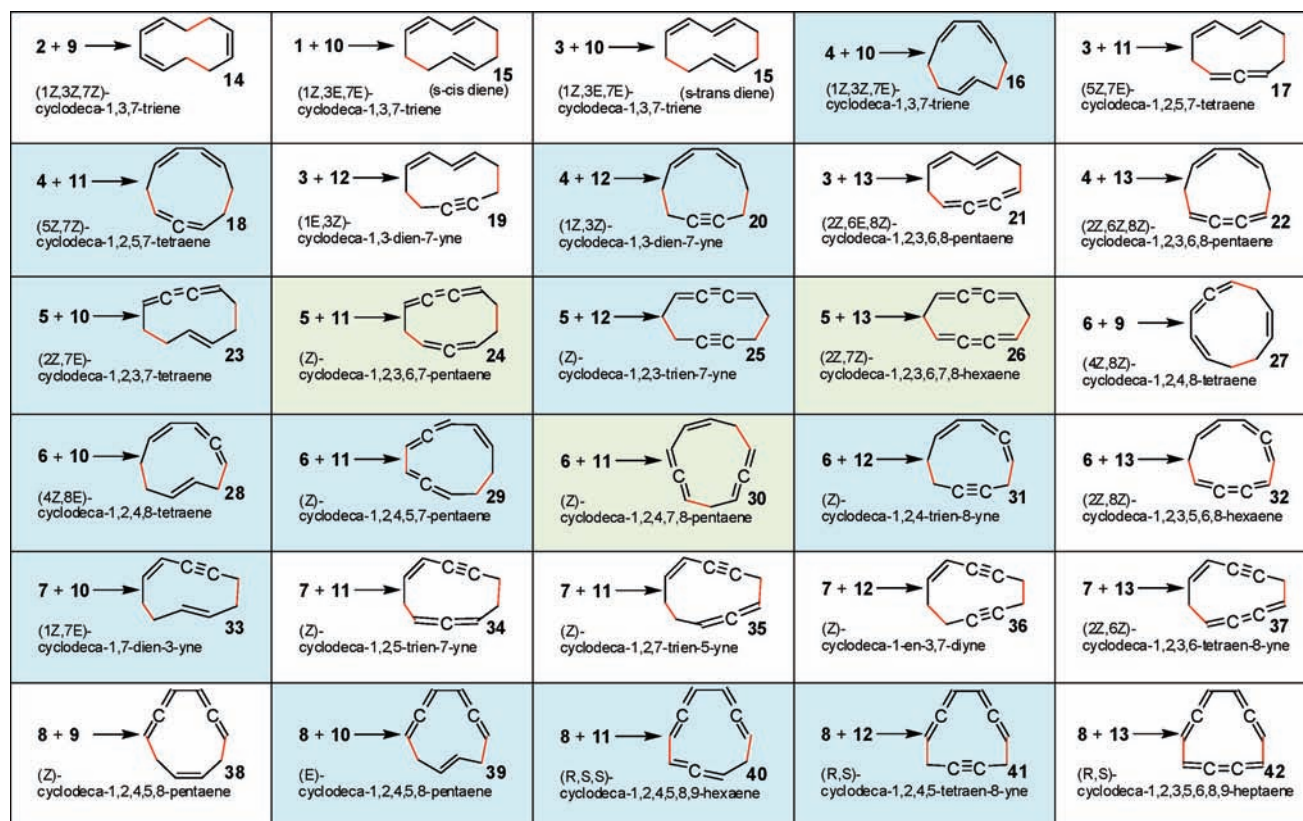
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Scheme 2. 6 + 4 Cycloadditions Resulting from Reaction of 6 $\pi$  Reactants 1–8 with 4 $\pi$  Reactants 9–13<sup>a</sup>

<sup>a</sup> The  $\sigma$ -bonds formed in each cycloaddition are shown in red. For all cases shaded blue, practical examples containing substituents are proposed later. Cases shaded green are followed by unusual rearrangements.

The cases shaded green are predicted to occur but to be immediately followed by intriguing rearrangements.

It is impractical in this paper to examine every unsubstituted case in Scheme 2, discover the problems, and then discuss how substituents might be used to overcome them. We will proceed as follows:

1. We examine the hexatriene/butadiene reactions leading to **14**–**16** in detail and show how substituents can be used to create practical examples.

2. We use the reaction leading to **25** to compare electronic effects in 6 + 4 and 4 + 2 reactions. This reaction is a stretched (diethynologous) analogue of the 4 + 2 reaction leading to cyclohexene.

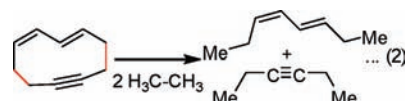
3. We will only discuss representative substituted examples of **18**, **20**, **23**, **24**, **28**, **29**, **30**, **31**, **33**, **39**, **40**, and **41**, showing how substituents can (a) overcome problems such as competing 4 + 2 cycloadditions and rapid Cope rearrangement of products and (b) lower activation energies.

Note that, in Scheme 2, (1Z,3E,7E)-cyclodeca-1,3,7-triene (**15**) is shown as arising from reaction of *s-trans*-butadiene (**10**) with both conformation **1** of (*Z*)-hexatriene and conformation **3** of the (*E*)-isomer. In fact, the first leads to a conformation of **15** containing an *s-cis* diene unit, while the second leads to a conformation with an *s-trans* diene, and these conformations are not interconvertible. At this point we emphasize that it is often difficult to draw the products clearly in realistic conformations, largely because the double bonds are frequently oriented more or less perpendicular to the general ring plane. Three-dimensional representations of all important products are shown later.

Table 1 lists the cycloadditions we have examined involving (*Z*)- and (*E*)-1,3,5-hexatrienes **1**–**4**. The first entry is for the cycloaddition of *s-cis,s-cis*-(*Z*)-hexa-1,3,5-triene with *s-cis*-butadiene to give (1Z,3Z,7Z)-cyclodeca-1,3,7-triene, for which a computed activation energy has been reported.<sup>10</sup> As Table 1 shows, there are better alternatives, some with activation energies comparable with that calculated for the cyclopentadiene/tropone reaction (87 kJ mol<sup>-1</sup>).<sup>10</sup>

The 20 basic types of 6 + 4 cycloadditions discussed in this paper involving 6 $\pi$  components **5**–**8** are summarized in Table 2.

Tables 1 and 2 list the strain energy in the products calculated at the B3LYP/6-31G\* level as the energy change in a standard isodesmic reaction, illustrated in eq 2 for the case of cyclodeca-1,3-dien-7-yne. In this formal reaction, the two  $\sigma$ -bonds formed in the cycloaddition have been split by addition of two molecules of ethane. The strain in cyclodecane itself according to the type of process shown in eq 2 is 70.0 kJ mol<sup>-1</sup>, and so it is clear that none of the products in Tables 1 and 2 are outrageously strained.



**Reaction Energies, Activation Energies, and Transition States.** The relatively simple B3LYP/6-31G\* method appears to be remarkably good at predicting activation energies when compared with the G3(MP2) method (compare the  $\Delta E^\ddagger$  values in Tables 1 and 2), and this gives us confidence in applying the



**Table 1.** Cycloadditions with Hexatrienes 1–4

reactants		product	B3LYP			G3(MP2)	
6 $\pi$	4 $\pi$		strain <sup>a</sup>	$\Delta E^a$	$\Delta E^\ddagger$ <sup>a</sup>	$\Delta E^a$	$\Delta E^\ddagger$ <sup>a</sup>
2	9	(1Z,3Z,7Z)-cyclodeca-1,3,7-triene ( <b>14</b> )	61	-62	139		
1	10	(1Z,3E,7E)-cyclodeca-1,3,7-triene ( <b>15</b> ) <sup>b</sup>	77	-61	114		
3	10	(1Z,3E,7E)-cyclodeca-1,3,7-triene <b>15</b>	60	-62	96	-91	81
4	10	(1Z,3Z,7E)-cyclodeca-1,3,7-triene ( <b>16</b> )	44	-78	110		
3	11	(5Z,7E)-cyclodeca-1,2,5,7-tetraene ( <b>17</b> )	40	-112	92	-123	90
4	11	(5Z,7Z)-cyclodeca-1,2,5,7-tetraene ( <b>18</b> )	35	-112	111		
3	12	(1E,3Z)-cyclodeca-1,3-dien-7-yne <b>19</b>	52	-101	83	-145	68
4	12	(1Z,3Z)-cyclodeca-1,3-dien-7-yne <b>20</b>	45	-110	105		
3	13	(2Z,6E,8Z)-cyclodeca-1,2,3,6,8-pentaene ( <b>21</b> )	70	-123	84	-127	81
4	13	(2Z,6Z,8Z)-cyclodeca-1,2,3,6,8-pentaene ( <b>22</b> )	66	-127	104		

<sup>a</sup> In kJ mol<sup>-1</sup>. <sup>b</sup> A relatively unstable *s-cis* conformation of the diene unit is formed in this reaction.

**Table 2.** Basic 6 + 4 Cycloadditions with Reactants 5–8

reactants		product	B3LYP			G3(MP2)	
6 $\pi$	4 $\pi$		strain <sup>a</sup>	$\Delta E^a$	$\Delta E^\ddagger$ <sup>a</sup>	$\Delta E^a$	$\Delta E^\ddagger$ <sup>a</sup>
5	10	(2Z,7E)-cyclodeca-1,2,3,7-tetraene ( <b>23</b> )	53	-66	103	-78	101
5	11	(Z)-cyclodeca-1,2,3,6,7-pentaene ( <b>24</b> )	22	-121	88	-114	95
5	12	(Z)-cyclodeca-1,2,3-trien-7-yne ( <b>25</b> )	40	-110	80	-135	75
5	13	(2Z,7Z)-cyclodeca-1,2,3,6,7,8-hexaene ( <b>26</b> )	43	-146	86	-115	92
6	9	(4Z,8Z)-cyclodeca-1,2,4,8-tetraene ( <b>27</b> )	67	-117	93	-125	96
6	10	(4Z,8E)-cyclodeca-1,2,4,8-tetraene ( <b>28</b> )	89	-94	98		
6	11	(Z)-cyclodeca-1,2,4,5,7-pentaene ( <b>29</b> )	68	-117	81	-109	89
6	11	(Z)-cyclodeca-1,2,4,7,8-pentaene ( <b>30</b> )	37	-146	87	-134	96
6	12	(Z)-cyclodeca-1,2,4-trien-8-yne ( <b>31</b> )	63	-129	87	-158	86
6	13	(2Z,8Z)-cyclodeca-1,2,3,5,6,8-hexaene ( <b>32</b> )	63	-167	87	-151	95
7	10	(1Z,7E)-cyclodeca-1,7-dien-3-yne ( <b>33</b> )	47	-115	78	-155	64
7	11	(Z)-cyclodeca-1,2,5-trien-7-yne ( <b>34</b> )	25	-162	73	-183	70
7	11	(Z)-cyclodeca-1,2,7-trien-5-yne ( <b>35</b> )	42	-145	82	-169	78
7	12	(Z)-cyclodeca-1-ene-3,7-diyne ( <b>36</b> )	51	-143	67	-197	52
7	13	(2Z,6Z)-cyclodeca-1,2,3,6-tetraen-8-yne ( <b>37</b> )	63	-169	72	-184	70
8	9	(Z)-cyclodeca-1,2,4,5,8-pentaene ( <b>38</b> )	63	-134	87	-128	92
8	10	(E)-cyclodeca-1,2,4,5,8-pentaene ( <b>39</b> )	86	-112	85		
8	11	(R,S,S)-cyclodeca-1,2,4,5,8,9-hexaene ( <b>40</b> )	66	-157	67	-134	78
8	12	(R,S)-cyclodeca-1,2,4,5-tetraen-8-yne ( <b>41</b> )	84	-146	74	-157	76
8	13	(R,S)-cyclodeca-1,2,3,5,6,8,9-heptaene ( <b>42</b> )	74	-193	72	-157	82

<sup>a</sup> In kJ mol<sup>-1</sup>.

former to the more complex and practical substituted cases discussed below. However, examination of Tables 1 and 2 shows that B3LYP/6-31G\* substantially underestimates the exothermicity of many 6 + 4 cycloadditions when compared to the usually reliable G3(MP2) method. It is well-known that B3LYP is not reliable with regard to the thermodynamics of the simplest of 4 + 2 cycloadditions.<sup>22</sup> Furthermore,  $\Delta E$  for the tropone/cyclopentadiene reaction is -37 kJ mol<sup>-1</sup> at the B3LYP/6-31G\* level but -111 kJ mol<sup>-1</sup> with G3(MP2). Thus, B3LYP/6-31G\* predicts this known reaction (eq 1) to be unfavorable (estimated  $\Delta G = +39$  kJ mol<sup>-1</sup> at 298 K). We discovered that the B3LYP/6-31G\* errors were not random but, surprisingly, correlated with the number of bonds created in the cycloaddition; this is discussed in more detail in the Supporting Information. The important point is that  $\Delta E$  values calculated by G3(MP2) are sufficiently negative that almost all the reactions are expected to be favorable (negative  $\Delta G$ ) at ambient and slightly elevated temperatures.

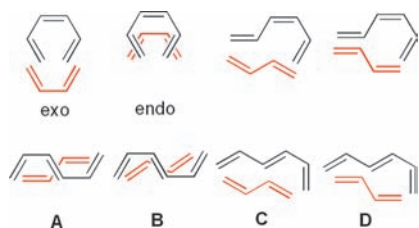
There was considerable variation in how synchronous formation of the two new  $\sigma$ -bonds was at the transition state (TS). Thus, cycloaddition of hexa-1,5-dien-3-yne (**5**) to butatriene (**12**) led to a TS with C<sub>s</sub> symmetry at the B3LYP/6-31G\* level, with both forming bonds 2.28 Å long, but many cycloaddition TSs

are markedly asynchronous. This variability is surprising, but we suspect that the energy surface is very flat near the TS (see the Supporting Information) so that rather subtle factors may be at work. In the limit, a nonsynchronous cycloaddition could involve diradical intermediates. Houk<sup>12</sup> has shown that such intermediates are probably involved in 6 + 4 reactions between cyclopentadiene and cycloheptatriene. Using unrestricted B3LYP/6-31G\* calculations with the guess=mix option, we had no difficulty in reproducing examples of Houk's diradicals, but we failed to find any examples of the 6 + 4 reactions described in this paper. This is consistent with the fact that nondynamic correlation in the TS structures was not found to be excessive based on the QCISD(T) calculations carried out as part of the G3(MP2) method. The reason for the difference from the cyclic systems is not clear.

**General.** Before proceeding to individual cycloadditions, we make some further general points:

1. Alternative 4 + 2 cycloadditions can compete with the 6 + 4 process wherever the 4 $\pi$  or 6 $\pi$  reactants can adopt a conformation with an *s-cis*-butadiene moiety, i.e., with butadiene itself and with 6 $\pi$  reactants **1–4**, **6**, and **7**. In many cases there are several possible competing 4 + 2 pathways, and we have computed activation energies for all of these (see the Supporting Information). In addition, 4 + 2 cycloadditions can usually occur by both exo and endo pathways; B3LYP/6-31G\* usually finds only small differences in  $\Delta E^\ddagger$  values for these.

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**Figure 2.** Approach geometries for the reaction of (*Z*)- and (*E*)-hexatrienes with butadiene.

2. Cope rearrangements of 6 + 4 products are usually favorable, and so it is clearly necessary to find TSs for all the possibilities, and we have done this (see the Supporting Information). In a number of cases, we show how to choose substituents that render Cope rearrangement unfavorable.

3. Our choice of cyano and maleimide substituent groups (see Scheme 1) has been partly dictated by computational convenience; other substituents with similar electronic properties may be expected to behave similarly, so long as they do not introduce extra steric problems.

4. All our calculations refer to the gas phase. We recognize that this is a serious limitation, particularly when polar substituents are present, but in a survey of this nature, applying realistic solution effects was not possible. Fortunately, polar 6 + 4 cycloadditions are likely to be accelerated in solution (and by Lewis acid catalysis, etc.), and we believe that destructive Cope rearrangements might actually be less susceptible to solvent effects and catalysis.

#### Cyclodeca-1,3,7-trienes from Hexatrienes and Butadienes.

Cycloaddition of hexatriene with butadiene produces cyclodeca-1,3,7-triene, and our study of this reaction led to a number of real surprises, which we list before engaging in detailed discussion.

(i) By far the most stable 6 + 4 product is (1*Z*,3*Z*,7*E*)-cyclodecatriene **16**, which contains one *trans*-double bond (and an *s-trans* diene unit).

(ii) The lowest activation energy process would lead to (1*Z*,3*E*,7*E*)-cyclodecatriene **15**, containing two *trans*-double bonds.

(iii) Both the 6 + 4 cycloadditions leading to the (1*Z*,3*Z*,7*E*)- and (1*Z*,3*E*,7*E*)-isomers involve using (*E*)-hexa-1,3,5-triene as reactant and butadiene in an *s-trans* conformation.

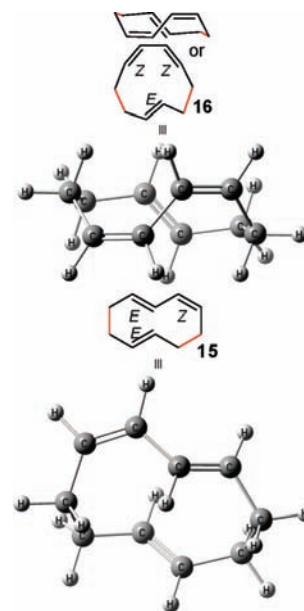
(iv) Both the cycloadditions in (iii) above share their TSs with 4 + 2 processes, and the 6 + 4/4 + 2 product outcome is decided at a subsequent valley/ridge inflection (VRI) point.

(v) Isolation of the 6 + 4 products above is unlikely to be possible in unsubstituted cases because Cope rearrangement to the 4 + 2 products is predicted to be too fast.

(vi) In spite of (v) above, 6 + 4 cycloadditions using substituted hexatrienes and butadienes may well be practical, especially those leading to (1*Z*,3*Z*,7*E*)-cyclodecatrienes.

**Cyclodeca-1,3,7-triene: Isomers and Conformers.** We carried out a full conformational search on all possible cyclodeca-1,3,7-trienes (see the Supporting Information), but, for the purpose of discussing low-energy 6 + 4 pathways, only the two lowest energy isomers, **15** and **16**, are important. (*Z*)-Cyclodecene is 15 kJ mol<sup>-1</sup> more stable than the (*E*)-isomer, but the most stable structure for the triene, **16** (*C*<sub>2</sub> symmetry), belongs to the (1*Z*,3*Z*,7*E*)-isomer family and contains an *s-trans* diene unit in addition to the *trans* double bond. No planar representation does justice to this intriguing structure, in which all the double bonds lie more or less perpendicular to the general plane of the 10-

membered ring. The energy difference between this structure and the next best conformer, an alternative *C*<sub>2</sub> (1*Z*,3*Z*,7*E*)-structure, is 15.2 kJ mol<sup>-1</sup>, an astonishingly high value, given that medium rings typically have many conformations of closely similar energy. This energy difference is comparable with that between chair and twist cyclohexane (estimated  $\Delta\Delta H = 19.7\text{--}26.0$  kJ mol<sup>-1</sup>). The third best conformer is the (1*Z*,3*E*,7*E*)-isomer **15**, at 16.3 kJ mol<sup>-1</sup>.

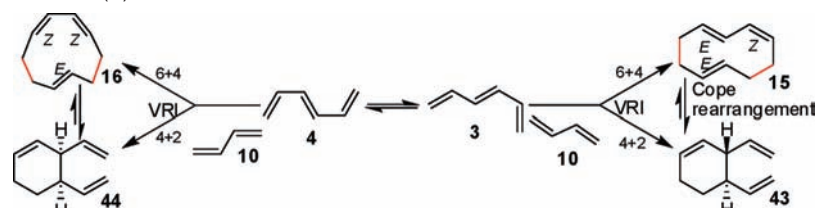


**6 + 4 Cycloaddition Transition States.** Possible approach geometries for the reaction of (*Z*)- and (*E*)-hexatrienes with butadiene are shown in Figure 2. Thus, the global minimum (1*Z*,3*Z*,7*E*)-conformer **16** is the product of approach geometry **A** in Figure 2, whereas an alternative *C*<sub>2</sub> (1*Z*,3*Z*,7*E*)-conformer ( $\Delta\Delta H = 15.2$  kJ mol<sup>-1</sup>) is the product of approach geometry **B**. Similarly (1*Z*,3*E*,7*E*)-conformer **15** results from approach geometry **C**, and an alternative conformer ( $\Delta\Delta H = 32.5$  kJ mol<sup>-1</sup>) results from approach geometry **D**. The terms “exo” and “endo” clearly apply to the reaction of *s-cis*,*s-cis*-(*Z*)-hexatriene with *s-cis*-butadiene, and it is predicted that the exo approach will be preferred.<sup>10</sup> Many other 6 + 4 additions also have alternative approach geometries corresponding with exo and endo, but that nomenclature is clearly inadequate, and in the Supporting Information we propose an alternative nomenclature based on like:unlike (*l:u*) nomenclature.<sup>23</sup>

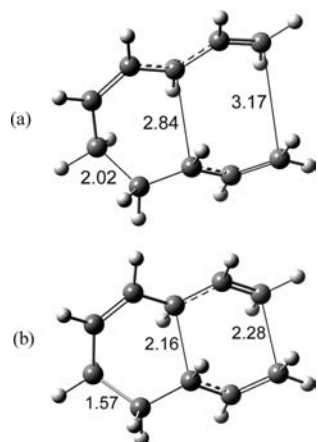
The lowest energy pathways for 6 + 4 reaction of (*E*)-hexatriene with *s-trans*-butadiene are shown in Scheme 3. If cycloaddition to give **16** could be achieved, it would be the first cycloaddition to yield a *trans*-cycloalkene product,<sup>24</sup> arising, of course, from reaction of a component in an *s-trans* conformation. If one considers cycloreversion of **16**, it can be seen that the conformation promises good overlap between the  $\pi$ -orbitals and the breaking C–C bonds. This, in turn, suggests a relatively favorable activation energy for the cycloaddition, and a B3LYP/6-31G\* search produces a TS with  $\Delta E^\ddagger = 110$  kJ mol<sup>-1</sup>, well below the  $\Delta E^\ddagger = 139$  kJ mol<sup>-1</sup> reported<sup>10</sup> for cycloaddition of *s-cis*,*s-cis*-(*Z*)-hexa-1,3,5-triene with *s-cis*-butadiene to give (1*Z*,3*Z*,7*Z*)-cyclodeca-1,3,7-triene. We note here that the most

(23) Seebach, D.; Prelog, V. *Angew. Chem., Int. Ed.* **1982**, *21*, 654–660.

(24) Bradley, A. Z.; Kociolk, M. G.; Johnson, R. P. *J. Org. Chem.* **2000**, *65*, 7134–7138.

Scheme 3. Cycloaddition Reaction of (*E*)-Hexatriene with *s*-*trans*-Butadiene<sup>a</sup>

<sup>a</sup> The pathway leading to **16** and **44** goes via approach A in Figure 2, while **15** and **43** arise from approach C.



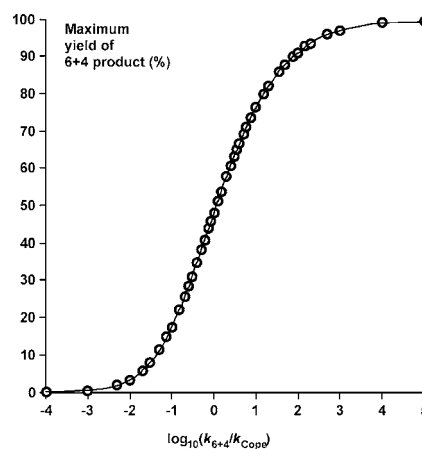
**Figure 3.** (a) Transition state for the formation of **15** and **43**. (b) Cope TS for the interconversion of **15** and **43**. Distances are in Å.

favorable cycloaddition using (*Z*)-hexa-1,3,5-triene is from the *s*-*cis*,*s*-*trans* conformer, but this has a B3LYP/6-31G\* activation energy of 114 kJ mol<sup>-1</sup> (second entry in Table 1).

(1*Z*,3*E*,7*E*)-Cyclodeca-1,3,7-triene (**15**) arises from *s*-*cis*,*s*-*trans*-(*E*)-hexatriene and *s*-*trans*-butadiene, and a B3LYP/6-31G\* search produces a TS with  $\Delta E^\ddagger = 96$  kJ mol<sup>-1</sup>, comparable to the calculated  $\Delta E^\ddagger$  (87 kJ mol<sup>-1</sup>) for the cyclopentadiene/tropone reaction. Again there is good overlap between  $\pi$ -orbitals and the breaking C–C bonds for cyclorversion of **15**, but why is  $\Delta E^\ddagger$  for this cycloaddition 14 kJ mol<sup>-1</sup> lower than for the process leading to the more stable isomer **16**? We suggest that a clue comes from the nonsynchronous nature of the TSs leading to **15** (see Figure 3a) and **16**. In both series, formation of one new  $\sigma$ -bond is quite advanced at the TS, but the other interactions are still weak, so the “outer” part of the hexatriene closely resembles a butadiene, which is *s*-*trans* for the more favorable TS leading to **15** but *s*-*cis* for that leading to **16**. The accepted energy difference between *s*-*trans*- and *s*-*cis*-butadiene is 14 kJ mol<sup>-1</sup>.

The intricacies of these reactions do not end there because, to our surprise, we were unable to find separate TSs for 6 + 4 and 4 + 2 pathways leading to **15** and **43**. Instead, the two processes share a common TS (Figure 3a), which is followed by a VRI point<sup>25–27</sup> where the two pathways diverge. The same situation arises in the reactions leading to **16** and **44**, and further details concerning the VRI are given in the Supporting Information.

Is this 6 + 4 cycloaddition a viable synthetic route to **15**? No! Cope rearrangement of **15** to **43**, via the TS shown in Figure



**Figure 4.** Maximum % 6 + 4 product C, based on consecutive cycloaddition (A + B → C) and Cope rearrangement (C → D) when  $[A]_0 = [B]_0 = 4$  M.

3b, is much too fast, with  $\Delta E^\ddagger = 109$  kJ mol<sup>-1</sup> (B3LYP/6-31G\*). Using computed  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$  values, we have roughly estimated second-order rate constants for the cycloaddition and first-order rate constants for the Cope rearrangement over a range of temperatures. In terms of favoring the bimolecular 6 + 4 process over the unimolecular Cope rearrangement, conducting the reactions under pseudo-first-order conditions by employing a high concentration, and thus a large excess, of one reactant is a highly beneficial strategy. Of course, this will prove satisfactory only when the component in large excess does not undergo cycloaddition reactions with itself. For reactants where this is a problem, using the highest concentration of both reactants will then be the best strategy. For this more general case we have assumed that, for reactants of this molecular mass, 4 M concentrations are probably attainable and computed the maximum % cycloaddition product as a function of  $\log_{10}(k_{6+4}/k_{\text{Cope}})$  (Figure 4). For the case leading to **15** and **43**,  $\log_{10}(k_{6+4}/k_{\text{Cope}})$  is always less than  $-4$ , so **15** would never be observed. The situation is not quite so clear-cut for the reactions leading to **16** and **44**, but, even so, only a few % of **16** might be observed at best.

The conclusion must be that, despite the intriguing features of these reactions, cycloaddition of the parent hexatrienes and butadienes can never lead to the isolation of the 6 + 4 product. Nevertheless, we show below that it should be practical to prepare suitably substituted derivatives of (1*Z*,3*Z*,7*E*)-cyclodecatriene (**16**) by 6 + 4 cycloaddition. The situation for derivatives of (1*Z*,3*E*,7*E*)-isomer **15** is less clear and is discussed in the Supporting Information.

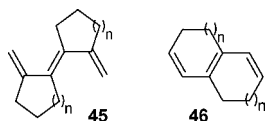
**Substituted (1*Z*,3*Z*,7*E*)-Cyclodeca-1,3,7-trienes via Conformationally Restrained Hexatrienes.** The only tactic that will guarantee reactions via the *s*-*cis*,*s*-*cis* conformer of the hexatriene is to introduce cyclic constraints, and we initially considered reactants based on trienes **45** and **46** for this purpose.

(25) Sadasivam, D. V.; Prasad, E.; R. A.; Flowers, I.; Birney, D. M. *J. Phys. Chem. A* **2006**, *110*, 1288–1294.

(26) Caramella, P.; Quadrelli, P.; Toma, L. *J. Am. Chem. Soc.* **2002**, *124*, 1130–1131.

(27) Quadrelli, P.; Romano, S.; Toma, L.; Caramella, P. *Tetrahedron Lett.* **2002**, *43*, 8785–8789.





However substitution of the terminal atoms in the triene, as in **46**, means that these substituents both lose conjugation as 6 + 4 cycloaddition takes place, and  $\Delta E$  for addition of 2,3-dicyanobutadiene to **45**,  $n = 1$ , is 83 kJ mol<sup>-1</sup> more favorable than for addition to **46**,  $n = 1$ , so we have only explored reactants based on the **45** skeleton. **This point is of general importance:** terminal substitution of either reactant reduces the exothermicity of a 6 + 4 cycloaddition and may make it impractical. Further examples will be discussed later.

Some examples of 6 + 4 cycloaddition to analogues of **45** are shown in Scheme 4. The B3LYP/6-31G\* activation energy for reaction of the bicyclopentane derivative **47** is still high, but alternative cycloadditions do not compete. Furthermore, Cope rearrangement of the product is now energetically unfavorable because, after Cope rearrangement, the substituents become isolated from the conjugation or hyperconjugation. Reaction of 2,3-dicyanobutadiene<sup>28,29</sup> with **47** is much faster,  $\Delta E^\ddagger = 41$  kJ mol<sup>-1</sup>, and this appears to be a very promising candidate for experimental test. Note that this diene strongly favors the *s-trans* conformation due to dipole repulsion in the *s-cis* conformation, which is calculated to be 25 kJ mol<sup>-1</sup> less stable. The two dilactones **48** and **49** make a striking pair. The activation energy for reaction of **48** is still high, and 4 + 2 cycloaddition of *s-cis*-butadiene to the carbonyl-activated terminal double bond is competitive ( $\Delta E^\ddagger = 73$  kJ mol<sup>-1</sup>).  $\Delta E^\ddagger$  for 6 + 4 is strikingly lowered to 41 kJ mol<sup>-1</sup> with dilactone **49**, and 4 + 2 addition of butadiene to the terminal double bond does not compete ( $\Delta E^\ddagger = 68$  kJ mol<sup>-1</sup>), so this would appear also to be a good case for experimental test. Diimide derivative **50** has an intermediate  $\Delta E^\ddagger$  and again should be practical.

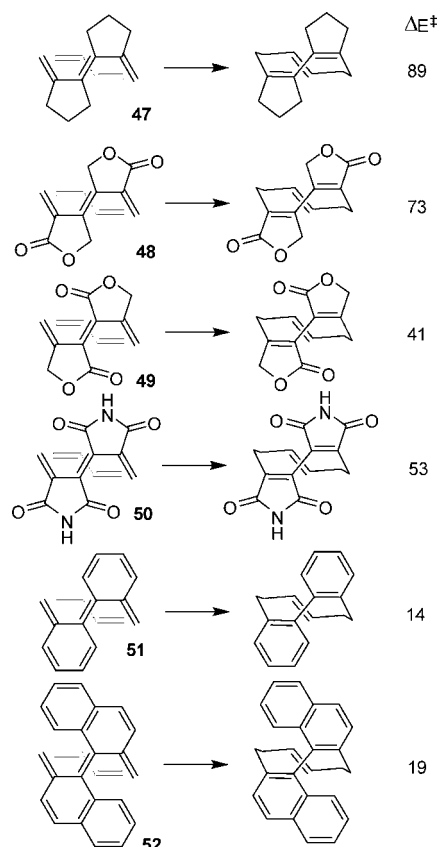
The double quinodimethane **51** is even more dramatic: the activation energy is so low that it is reasonable to expect that, if **51** could be generated by a suitable fragmentation reaction in the presence of butadiene, it would be immediately trapped, leading to (1*Z*,3*Z*,7*E*)-dibenzo[*a,c*]cyclodecatriene. The dinaphthotriene **52** might be generated in chiral form from known (*R*)- or (*S*)-2,2'-dibromomethyl-1,1'-binaphthalene,<sup>30</sup> leading to a chiral (1*Z*,3*Z*,7*E*)-cyclodecatriene.

We studied a series of heterocyclic analogues of **51** that could provide (1*Z*,3*Z*,7*E*)-cyclodecatrienes suitable for further functionalization and found that calculated activation energies correlate inversely with the aromaticity of the heterocycles, as might be expected.

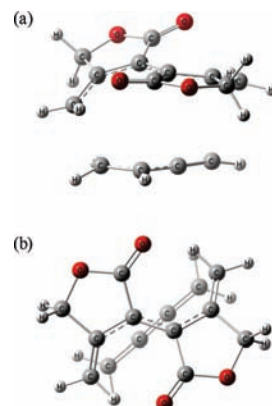
To summarize this section, we have seen that hexatriene/butadiene reactions can lead to intriguing derivatives of (1*Z*,3*Z*,7*E*)-cyclodecatriene (**16**) when substituents are introduced that provide activation but simultaneously control or avoid competing reactions.

**Cyclodeca-1,2,5,7-tetraenes, Cyclodeca-1,3-dien-7-yne, and Cyclodeca-1,2,3,6,8-pentaenes.** Cyclodeca-1,2,5,7-tetraene is the product of 6 + 4 cycloaddition between hexatriene and butenyne (**11**), cyclodeca-1,3-dien-7-yne arises from hexatriene and butatriene (**12**), and cyclodeca-1,2,3,6,8-pentaene results from

**Scheme 4.** 6 + 4 Cycloadditions to Constrained Derivatives of (3*E*)-Hexatriene<sup>a</sup>



<sup>a</sup> Activation energies are in kJ mol<sup>-1</sup>.



**Figure 5.** Transition states (a) for reaction of dilactone **49** with butenyne (**11**) and (b) for reaction of dilactone **49** with butatriene (**12**).

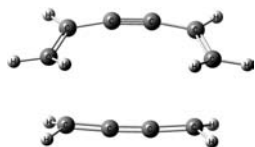
hexatriene and butadiyne (**13**). Just as with the hexatriene/butadiene reaction, the lowest TSs in all cases involve *s-cis,s-trans*-(*E*)-hexatriene, and the products are predicted to undergo very rapid Cope rearrangement to give six-membered-ring products (see the Supporting Information for details). However, we predict that conformationally restricted (*E*)-hexatrienes can lead to successful 6 + 4 cycloaddition.

Figure 5a shows the TS for reaction of dilactone **49** (necessarily *s-cis,s-cis*) with butenyne to give a (5*Z*,7*Z*)-cyclodeca-1,2,5,7-tetraene. The activation energy is low (50 kJ mol<sup>-1</sup>), and Cope rearrangement of the product is now unfavorable, so we believe that the 6 + 4 product would be isolable. It is interesting that, at the TS, the forming sp<sup>3</sup>-sp<sup>3</sup> bond is much

(28) Bellus, D.; Weis, C. D. *Tetrahedron Lett.* **1973**, 999–1000.

(29) Bellus, D.; Bredow, K. V.; Sauter, H.; Weis, C. D. *Helv. Chim. Acta* **1973**, *56*, 3004–3038.

(30) Mazaleyrat, J. P.; Wakselman, M. *J. Org. Chem.* **1996**, *61*, 2695–2698.



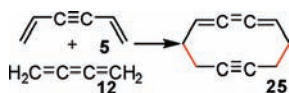
**Figure 6.** B3LYP/6-31G\* transition state for cycloaddition of hexa-1,5-dien-3-yne with butatriene.

shorter (2.18 Å) than the forming  $sp^3$ – $sp^2$  bond (2.79 Å); this is the reverse of the situation with the parent *s-cis,s-trans* triene and is the only example we have found where bonding to the alkene carbon of butenyne runs ahead of bonding to the alkyne center. Reaction of butenyne with diimide **50**,  $\Delta E^\ddagger = 61$  kJ mol<sup>-1</sup>, would also be expected to produce the 6 + 4 product, and diquinodimethane **51** is predicted to be efficiently trapped by butenyne ( $\Delta E^\ddagger = 17$  kJ mol<sup>-1</sup>), so a range of similar reactions would be expected to yield 6 + 4 products with intriguing stereochemistry.

The TS for reaction of dilactone **49** with butatriene has  $C_2$  symmetry (Figure 5b), with forming bonds 2.46 Å long and  $\Delta E^\ddagger = 39$  kJ mol<sup>-1</sup>, while diimide **50** produces a  $C_1$  TS with forming bonds 2.23 and 2.54 Å long and  $\Delta E^\ddagger = 52$  kJ mol<sup>-1</sup>. These would appear to be viable 6 + 4 cycloadditions. Finally, butatriene is predicted to react with diquinodimethane **51** almost without activation ( $\Delta E^\ddagger = 7$  kJ mol<sup>-1</sup>).

Practical syntheses of cyclodeca-1,2,3,6,8-pentaenes might also be achievable. Thus, dilactone **49** reacts with butadiyne **13** via a  $C_2$  TS ( $\Delta E^\ddagger = 49$  kJ mol<sup>-1</sup>), while for diimide **50**  $\Delta E^\ddagger = 59$  kJ mol<sup>-1</sup> ( $C_1$  TS with forming bonds 2.04 and 3.17 Å). For diquinodimethane **51**,  $\Delta E^\ddagger = 18$  kJ mol<sup>-1</sup>, and the TS has  $C_2$  symmetry again. Note that all these activation energies are larger than the corresponding ones for butatriene; this appears to be a general trend for other 6 + 4 cycloadditions involving this pair of  $4\pi$  reactants. Also the products of the reactions with butadiyne are still butatrienes and might undergo a second 6 + 4 cycloaddition. For these reasons, we have not counted these cases as “practical”.

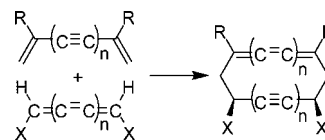
**Cycloadditions to Hexa-1,5-dien-3-yne (5). (Z)-Cyclodeca-1,2,3-trien-7-yne: A Comparison of Substituent Effects.** The reaction of **5** with butatriene (**12**) provides a particularly good opportunity to compare electronic substituent effects with its well-known 4 + 2 counterpart.



Cycloaddition of hexa-1,5-dien-3-yne (**5**) with butatriene **12** to give **25** is thermodynamically favorable (Table 1) and has a relatively low activation energy ( $\Delta E^\ddagger = 80$  kJ mol<sup>-1</sup>). The B3LYP/6-31G\* TS (Figure 6) has  $C_s$  symmetry and one imaginary frequency (i489 cm<sup>-1</sup>); the two forming bonds are 2.28 Å long. Thus, this reaction has all the characteristics of a “stretched” (diethynologous) version of the prototype 4 + 2 cycloaddition of butadiene with ethene. Potential competing 4 + 2 reactions all yield extremely strained cyclic allenes and can be ignored. We considered the possibility of antarafacial, antarafacial cycloaddition in this case, but the B3LYP/6-31G\*  $\Delta E^\ddagger$  is enormous (204 kJ mol<sup>-1</sup>). Orbital overlap is much poorer, and we believe that this will be a general problem for antarafacial, antarafacial 6 + 4 cycloadditions.

We have compared the activating effects of substituents on the “stretched” 6 + 4 reaction described above with the proto-

**Scheme 5.** 4 + 2 ( $n = 0$ ) and 6 + 4 ( $n = 1$ ) Cycloadditions



**Table 3.** Substituent Effects in 4 + 2 and 6 + 4 Reactions

R = X =	H H	H CN	CN H	CN CN	CN Me	Me CN
$n = 0$						
$\Delta E^{\ddagger a}$	104	91	88	107	104	86
$\Delta E$	-154	-135	-172	-125	-147	-141
partial bond, Å	2.27	2.26	2.30	2.27	2.29	2.26
$n = 1$						
$\Delta E^\ddagger$	80	76	58	78	70	74
$\Delta E$	-110	-68	-142	-77	-119	-74
shorter partial bond, Å	2.28	2.10	2.32	2.10	2.12	2.02
longer partial bond, Å	2.28	2.44	2.32	2.50	2.61	2.60

<sup>a</sup> All energies are from B3LYP/6-31G\* calculations and are in kJ mol<sup>-1</sup>.

type 4 + 2 cycloaddition of butadiene with ethene. For simplicity, we have used cyano and methyl as substituents, retained symmetrical substitution, and examined only exo orientation. The reactions are shown in Scheme 5, and results are shown in Table 3. All the 4 + 2 cycloadditions are synchronous with  $C_s$  TSs, while the 6 + 4 cycloaddition TSs are either synchronous or only moderately nonsynchronous. B3LYP activation energies for the 6 + 4 cycloadditions are consistently lower than for the corresponding 4 + 2 reactions, which is encouraging.

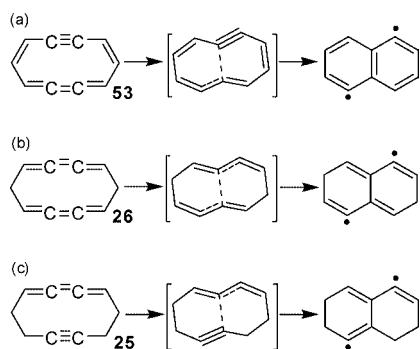
Houk has reported that B3LYP underestimates the activating effect of cyano groups in a series of reactions of cyanoethenes with cyclopentadiene and that MPW1K performs better.<sup>31</sup> We carried out MPW1K/6-311G\*\*//B3LYP/6-31G\* calculations for all the cases in Table 3 but found that only for the 4 + 2 cases are the energies significantly different, and then only when the cyano groups were on terminal atoms that were rehybridizing from  $sp^2$  to  $sp^3$ , and thus losing conjugation. For simplicity, we report only the B3LYP/6-31G\* results here.

In general, cyano substituents lower activation energies when placed in either the larger ( $4\pi$  or  $6\pi$ ) or smaller ( $2\pi$  or  $4\pi$ ) reactant, in accord with the ideas of “normal” and “inverse electron demand” Diels–Alder cycloaddition theory (see the Supporting Information for further comment). Placing cyano groups in both reactants either has little effect or actually raises activation energies. Part of the explanation for the latter may be that, where cyano groups are going out of conjugation as a result of cycloaddition, there is a substantial (30 – 40 kJ mol<sup>-1</sup>) decrease in the exothermicity of the reaction. It might be expected from the standard frontier orbital interpretation that Me, CN combinations would have lower activation energies than the corresponding H, CN reactions. There are minor effects in that direction when the methyl substituent is in a nonterminal position, but when Me is terminal, activation energies rise. This probably is the result of loss of hyperconjugation and is reflected in decreased exothermicity.

While discussion of the trends in Table 3 is interesting, the most important conclusion is that the best 6 + 4 reaction in Table 3 (R = H, X = CN,  $\Delta E^\ddagger = 58$  kJ mol<sup>-1</sup>) is fully

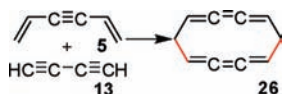
(31) Jones, G. O.; Guner, V. A.; Houk, K. N. *J. Phys. Chem. A* **2006**, *110*, 1216–1224.



**Scheme 6.** Unimolecular Cyclizations to Biradicals

synchronous and is predicted to be much faster than the corresponding 4 + 2 reaction ( $\Delta E^\ddagger = 88 \text{ kJ mol}^{-1}$ ). This 6 + 4 cycloaddition would occur at a useful rate at 50–100 °C, but butatriene would be a gas under those temperatures. The corresponding reaction with  $\text{CO}_2\text{Me}$  substituents is predicted to have  $\Delta E^\ddagger = 50 \text{ kJ mol}^{-1}$ , should proceed at ambient temperatures, and would appear to be practical.

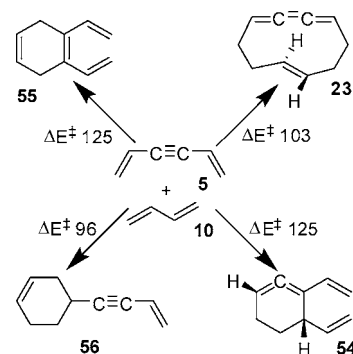
**(2Z,7Z)-Cyclodeca-1,2,3,6,7,8-hexaene and Its Transannular Bicyclization.** Cycloaddition of unsubstituted hexa-1,5-dien-3-yne (**5**) with butadiyne (**13**) is the “stretched” analogue of the butadiene plus ethyne 4 + 2 reaction. It is clearly favorable thermodynamically and has an activation energy of  $83 \text{ kJ mol}^{-1}$  at the B3LYP/6-31G\* level (Table 1), while potentially competing 4 + 2 reactions all yield extremely strained cyclic allenes and can be ignored. The TS has one imaginary frequency ( $i461 \text{ cm}^{-1}$ ), and the two forming bonds have lengths of 1.99 and 2.73 Å. Although the TS is highly nonsynchronous, we could find no evidence for diradical character. Substituent effects on this reaction are described in the Supporting Information.



(2Z,7Z)-Cyclodeca-1,2,3,6,7,8-hexaene (**26**) and (Z)-cyclodeca-1,2,3-trien-7-yne (**25**) are quite similar in structure to dehydroannulene (**53**), which Myers<sup>32</sup> showed to undergo exceedingly rapid transannular reaction followed by hydrogen abstraction to yield naphthalene. Schreiner<sup>33</sup> has also recently discussed the cyclization of some 1,2-didehydro[10]annulenes.

We made a comparative study of the unimolecular cyclizations of **53**, **26**, and **25** (see Scheme 6). Modeling the cyclization of **53** with unrestricted B3LYP/6-31G\* calculations leads to an activation energy of  $88 \text{ kJ mol}^{-1}$ , somewhat higher than the experimental value of  $68 \text{ kJ mol}^{-1}$ . The TS has  $s^2 = 0.00$ , indicating that it is still a closed-shell species. Cyclization leads to a singlet diradical ( $s^2 = 0.91$ ) that is protected from reverse ring-opening by a barrier of  $72 \text{ kJ mol}^{-1}$ . Clearly this will have a long enough lifetime that it can abstract hydrogen from the solvent to yield naphthalene, as is observed.

The ring-closure of **26** is calculated to have a rather similar barrier of  $91 \text{ kJ mol}^{-1}$ , and the biradical ( $s^2 = 0.91$ ) product is still protected by a substantial barrier of  $54 \text{ kJ mol}^{-1}$  from

**Scheme 7.** Cycloaddition Reactions of Hexa-1,5-dien-3-yne with Butadiene<sup>a</sup>

<sup>a</sup> Activation energies ( $\text{kJ mol}^{-1}$ ) are from B3LYP/6-31G\* calculations.

reopening, so we suggest that **26** will behave like **53**. In this case the TS does have significant diradical character ( $s^2 = 0.16$ ). Ring-closure of **25** requires a substantially higher activation energy of  $120 \text{ kJ mol}^{-1}$ , and the singlet diradical ( $s^2 = 0.89$ ) formed is much less stable (reverse ring-opening barrier of  $28 \text{ kJ mol}^{-1}$ ), so **25** should have a useful lifetime at ambient temperatures. We also examined the alternative cyclizations of **53**, **26**, and **25** that lead to 5,7-ring systems, but these are all much less favorable.

We suggest that, while **26** is likely to undergo unimolecular cyclization, **25** and most other 6 + 4 products should be stable in this respect, but controlled transannular reactions with external reagents could be carried out which could be more productive synthetically, although we have not made a study of these.

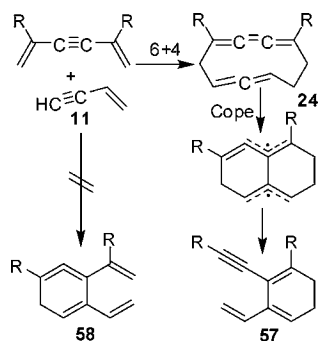
**Cyclodeca-1,2,3,7-tetraenes.** Potential reactions of hexa-1,5-dien-3-yne (**5**) with *s-trans*-butadiene (**10**) are shown in Scheme 7. Cyclic allene **54** is very strained, and  $\Delta E$  for this reaction is  $61 \text{ kJ mol}^{-1}$  less favorable than for the 6 + 4 process leading to **23** at the B3LYP/6-31G\* level. The TS leading to **23** is nonsynchronous, with forming bond lengths of 2.00 and 2.57 Å; it has one imaginary frequency of  $i500 \text{ cm}^{-1}$ .

*s-cis*-Butadiene can, of course, undergo 4 + 2 reactions with either the alkene or the alkyne functions in the hexadienyne. At the B3LYP/6-31G\* level, 4 + 2 reaction with the alkyne to give **55** is the most exothermic reaction but also has the highest activation energy and is not competitive with the 6 + 4 process. However, 4 + 2 reaction with the terminal alkene to give **56** has the lowest activation energy by  $7 \text{ kJ mol}^{-1}$ . Thus, to favor the 6 + 4 process, it will be necessary to use butadiene derivatives which strongly prefer the *s-trans* geometry. This is also the one case where cycloaddition is only marginally favorable thermodynamically, with  $\Delta E$  calculated to be only  $-78 \text{ kJ mol}^{-1}$  by G3(MP2). The reactivity of a series of substituted hexa-1,5-dien-3-yne with butadienes is discussed in the Supporting Information, but we found that the best case is that with 2,3-dicyanobutadiene. We predict that this will react with 2,5-dimethylhexa-1,5-dien-3-yne with  $\Delta E^\ddagger = 68 \text{ kJ mol}^{-1}$ ; 4 + 2 reaction at the terminal double bond of the hexa-1,5-dien-3-yne is not competitive ( $\Delta E^\ddagger = 83 \text{ kJ mol}^{-1}$ ). The energy of reaction (B3LYP/6-31G\*  $\Delta E = -93 \text{ kJ mol}^{-1}$ ) is also significantly improved (the cyano groups remain in conjugation), and we suggest that this reaction is a practical one that should occur at a reasonable rate at  $\sim 100 \text{ }^\circ\text{C}$ .

**(Z)-Cyclodeca-1,2,3,6,7-pentaene.** Reaction of hexa-1,5-dien-3-yne (**5**) with butenyne (**11**) might give cyclodeca-1,2,3,6,7-

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(33) Navarro-Vazquez, A.; Schreiner, P. R. *J. Am. Chem. Soc.* **2005**, *127*, 8150–8159.

**Scheme 8.** Cycloaddition of a Hexa-1,5-dien-3-yne with **11** and Subsequent Cope Rearrangement

pentaene (**24**, R = R = H), but as Scheme 8 shows, this has a unique and intriguing escape route to give **57**, R = R = H.

B3LYP/6-31G\* predicts that the exo TS ( $\Delta E^\ddagger = 88$  kJ mol<sup>-1</sup>) leading to **24** is preferred to the endo ( $\Delta E^\ddagger = 93$  kJ mol<sup>-1</sup>). The exo TS has an imaginary frequency of i458 cm<sup>-1</sup> and is markedly asynchronous, with bond formation to the alkyne terminus of **11** running ahead of sp<sup>3</sup>-sp<sup>3</sup> bonding (forming bond lengths of 1.94 and 2.79 Å). Competing 4 + 2 reactions all yield extremely strained cyclic allenes (e.g., **58**), so this might seem a favorable case for experimental investigation. However, there is a unique Cope rearrangement of **24** involving the 2,3- and 6,7-double bonds, and rearrangement of **24**, R = R = H, to give **57**, R = R = H, is calculated to be so fast that the 6 + 4 product could never be isolated (two other Cope rearrangements lead to highly strained cyclohexa-1,2-dienes and can be ignored). Note that **57** is *not* a possible 4 + 2 product, and indeed two of the carbons atoms of the original hexa-1,5-dien-3-yne have become separated in **57**!

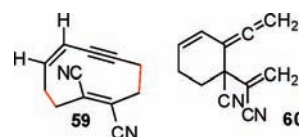
The Cope rearrangement of **24**, R = R = H, to give **57**, R = R = H, is actually predicted to be rather unusual mechanistically, as we found that there were two TSs separated by the (singlet) tetramethyleneethane diradical shown in Scheme 8.

This sequence of 6 + 4 cycloaddition followed by Cope rearrangement could be an interesting route to some highly functionalized 2,3-disubstituted cyclohexa-1,3-dienes. As might be expected, the 6 + 4 cycloaddition is strongly accelerated by the addition of ester and cyano groups to the hexadienyne ( $\Delta E^\ddagger = 56$  kJ mol<sup>-1</sup> for formation of **24**, R = R = CO<sub>2</sub>Me;  $\Delta E^\ddagger = 64$  kJ mol<sup>-1</sup> for **24**, R = R = CN). Cope rearrangement of **24**, R = R = CN, is still very fast ( $\log_{10}(k_{6+4}/k_{\text{Cope}}) = -2.9$  at 348 K), so the 6 + 4 product would not accumulate, but with **24**, R = R = CO<sub>2</sub>Me,  $\log_{10}(k_{6+4}/k_{\text{Cope}}) = -0.1$  at 348 K), so **24** might accumulate during the reaction but could easily be converted to **57**, R = R = CO<sub>2</sub>Me. Examples where the cycloaddition could be completed before Cope rearrangement set in would be advantageous, because the products **57** do have the potential to act as 4 + 2 dienes toward the starting materials.

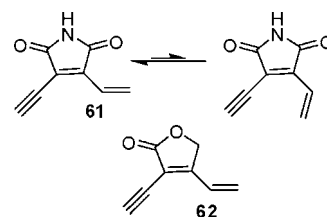
**Cycloadditions to Hexa-1,2,3,5-tetraene (7).** We explored the 6 + 4 reactions of hexa-1,2,3,5-tetraene<sup>34</sup> (**7**) with 4π reactants **10–13** and all the potential competing side reactions, but here we will only discuss one substituted case, since subsequent Cope rearrangements are generally so fast that the initial 10-membered ring products would never be seen. Further discussion can be found in the Supporting Informa-

tion, where energies and geometries for all the 6 + 4 cycloadditions and Cope rearrangements involving hexa-1,2,3,5-tetraene are listed.

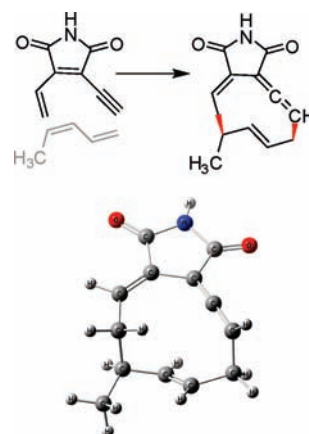
The 6 + 4 product might be observed in the reaction with 2,3-dicyanobutadiene.  $\Delta E^\ddagger$  for the 6 + 4 cycloaddition is only 56 kJ mol<sup>-1</sup>, suggesting that this reaction would occur at a reasonable rate at 50–100 °C.  $\log_{10}(k_{6+4}/k_{\text{Cope}}) = 2.5$  at 348 K, so the 6 + 4 product, 7,8-dicyanocyclodeca-1,7-dien-3-yne (**59**), would accumulate during the reaction; **59** is calculated to be 10 kJ mol<sup>-1</sup> less stable than the Cope rearrangement product 3-vinylidene-4-(1-cyanovinyl)-4-cyanocyclohex-1-ene (**60**).



**Cycloadditions to (Z)-Hexa-1,3-dien-5-yne (6).** Cycloadditions to (Z)-hexa-1,3-dien-5-yne (**6**) itself pose a range of problems (see the Supporting Information), and we discuss here only reactions of imide- and lactone-substituted reactants **61** and **62**. All the successful 6 + 4 cycloadditions occur from the less favorable *s-cis* conformation, but calculated energies are based on *s-trans* conformations as starting material (4 and 7 kJ mol<sup>-1</sup> more stable, respectively).

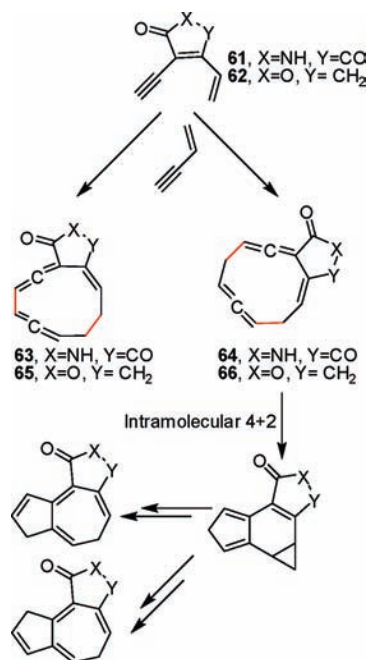


6 + 4 cycloaddition of **61** can occur to both *s-cis*- and *s-trans*-butadiene with similar activation energies (67 and 69 kJ mol<sup>-1</sup>), but 4 + 2 cycloaddition of the *s-cis* conformer to the alkyne of **61** is competitive. This problem is avoided in cycloaddition of **61** to *s-trans*-(Z)-pentaadiene, which is also predicted to occur readily ( $\Delta E^\ddagger = 66$  kJ mol<sup>-1</sup>) and will form the stereo- and regioisomer shown below, since bond formation to the sp center is relatively advanced at the TS and prefers the unsubstituted terminus of the pentaadiene. Experimental test of reactions related to these would appear to be justified.



6 + 4 cycloaddition of (Z)-hexa-1,3-dien-5-yne (**6**) to butenyne (**11**) can lead to either (Z)-cyclodeca-1,2,4,5,7-pentaene or (Z)-

(34) Maurer, H.; Hopf, H. *Angew. Chem., Int. Ed.* **1976**, *15*, 628–629.

**Scheme 9.** Reactions of **61** and **62** with Butenyne

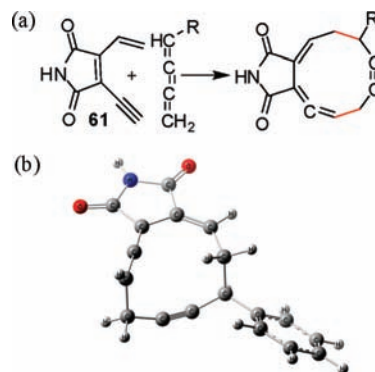
cyclodeca-1,2,4,7,8-pentaene. The unsubstituted cases are discussed in detail in the Supporting Information, and it is shown that potential 4 + 2 reactions do not compete but that (*Z*)-cyclodeca-1,2,4,7,8-pentaene will undergo a remarkable sequence of rearrangements: intramolecular 4 + 2 cycloaddition, followed by 1,5-sigmatropic shift, and retro-electrocyclization to give dihydroazulene products. In the unsubstituted case, the less interesting cyclodeca-1,2,4,5,7-pentaene is favored ( $\Delta E^\ddagger = 81$  vs  $87$  kJ mol<sup>-1</sup>), but it is shown that addition of terminal methyl groups to the alkynes of either reactant renders the activation energies for the two pathways essentially equivalent.

Scheme 9 shows the outcome for reaction of butenyne (**11**) with **61** and **62**. Reaction of butenyne with imide **61** favors the cyclodeca-1,2,4,5,7-pentaene product **63** over **64**, although only marginally ( $\Delta E^\ddagger = 56$  vs  $57$  kJ mol<sup>-1</sup>), while reaction with lactone **62** also just favors the cyclodeca-1,2,4,5,7-pentaene **65** over **66** ( $\Delta E^\ddagger = 71$  vs  $72$  kJ mol<sup>-1</sup>). The cyclodeca-1,2,4,7,8-pentaenes **64** and **66** will then rearrange as shown. These reactions would appear to be practical in the laboratory, and we predict that the addition of methyl groups to the alkynes of **61** or **62** (or to butenyne (**11**)) is likely to make the cyclodeca-1,2,4,7,8-pentaene pathway the preferred one, although we have not made detailed studies of this.

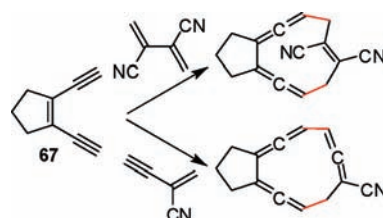
Reaction of imide **61** with butatriene (**12**) (Scheme 10, R = H,  $\Delta E^\ddagger = 61$  kJ mol<sup>-1</sup>) should occur at a satisfactory rate at 50–100 °C. To be practical, however, a less volatile substituted butatriene would have to be used. We have not optimized the TS for such a case, but the stereo- and regiochemistry can be predicted to be as shown in Scheme 10b, based on the early formation of the sp–sp<sup>2</sup> bond. The five-membered ring fusion enforces a conformation for the 10-membered ring in which the atoms that would have to bond in a Cope rearrangement are far apart (3.75 Å), so rearrangement is likely to be very slow.

Reaction of imide **61** with butadiyne (**13**) is somewhat less favorable than the butatriene reaction ( $\Delta E^\ddagger$  66 = kJ mol<sup>-1</sup>) but also might be practical.

**Cycloadditions to (*Z*)-Hexa-3-ene-1,5-diyne **8**.** Reactions of (*Z*)-hexa-3-ene-1,5-diyne represent extreme cases of unsatura-

**Scheme 10.** (a) Reaction of Imide **55** with Butatrienes<sup>a</sup> and (b) Likely Stereo- and Regiochemistry of the Product with R = Ph

<sup>a</sup> New  $\sigma$ -bonds are shown in red.

**Scheme 11.** Reaction of 1,2-Diethynylcyclopentene (**67**) with 2,3-Dicyanobutadiene and with 2-Cyanobutenyne

tion in these 6 + 4 cycloaddition products, and it may be doubtful if reactions of the parent (*Z*)-hexa-3-ene-1,5-diyne<sup>35,36</sup> (**8**) could be attempted, but all the basic reactions with 4 $\pi$  components **9**–**13** are detailed in the Supporting Information. One favorable feature of these reactions is that Cope rearrangements are not a problem, since the products would be highly strained six-membered ring allenes. As far as introducing substituents is concerned, it is unfortunate that the addition of substituents (e.g., trimethylsilyl groups) to the terminal alkyne positions that are known to provide much improved reactant stability also raises activation energies unacceptably. We have therefore examined (at the B3LYP/6-31G\* level) the reactions of 1,2-diethynylcyclopentene (**67**), as a known<sup>37</sup> and fairly stable derivative of **8**, and of imide derivative **68**, to see the effect of introducing electron-withdrawing groups in the 6 $\pi$  reactant.

6 + 4 cycloaddition of **67** with 2,3-dicyanobutadiene in an *s-trans* conformation (Scheme 11) has  $\Delta E^\ddagger = 55$  kJ mol<sup>-1</sup> and so should occur readily; 4 + 2 cycloaddition to a terminal alkyne does not compete. Note that the product has potential chirality, not because of the two allenes which are necessarily (*R,S*) but due to the *trans*-alkene with planar chirality. Alkene rotation would require passage of a cyano group through the 10-membered ring and can be ruled out. 6 + 4 cycloaddition of **67** to 2-cyanobutenyne (Scheme 11) has  $\Delta E^\ddagger = 62$  kJ mol<sup>-1</sup> and yields the substituted cyclodeca-1,2,4,5,8,9-hexaene shown.

The parent (*Z*)-hexa-3-ene-1,5-diyne (**8**) favors reaction with *s-cis*-butadiene, but imide derivative **68** favors reaction with the *s-trans*-butadiene isomer **10** ( $\Delta E^\ddagger = 67$  vs  $73$  kJ mol<sup>-1</sup>), probably because the terminal atoms in **68** are farther apart than in **8** (4.71 vs 4.48 Å). This reaction (Scheme 12) would merit practical test. The reaction of **68** with butenyne (**11**) ( $\Delta E^\ddagger =$

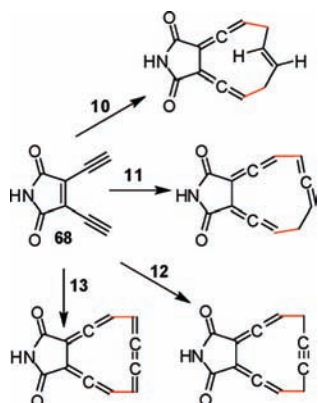
(35) Okamura, W. H.; Sondheim, F. *J. Am. Chem. Soc.* **1967**, *89*, 5991–5992.

(36) Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660–661.

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**Scheme 12.** Reaction of Imide **68** with *s-trans*-Butadiene, Butenyne (**11**), Butatriene (**12**), and Butadiyne (**13**)



54 kJ mol<sup>-1</sup>) yields a substituted cyclodeca-1,2,4,5,8,9-hexaene (see the Supporting Information for further comment). Reactions of **68** with butatriene (**12**) ( $\Delta E^\ddagger = 59$  kJ mol<sup>-1</sup>) and with butadiyne (**13**) ( $\Delta E^\ddagger = 63$  kJ mol<sup>-1</sup>) also appear feasible (Scheme 12).

## Conclusions

A number of important general points have emerged from this study:

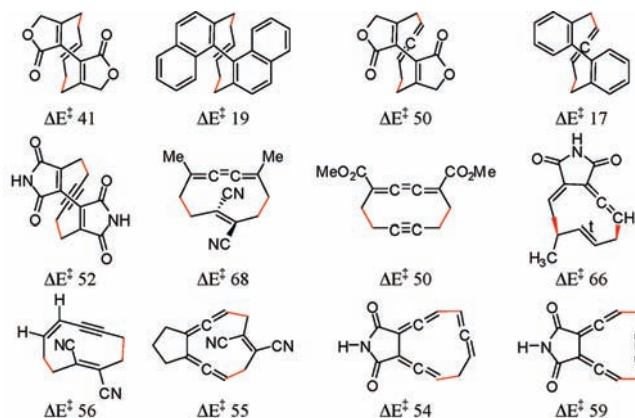
1. All the 30 basic 6 + 4 cycloadditions examined are favorable (exergonic) according to G3(MP2) calculations.
2. Cyclodecane derivatives containing *trans*-double bonds, *s-trans* diene units, alkynes, allenes, and cumulenes are possible products of 6 + 4 cycloadditions. Many have lower strain energies than cyclodecane itself, but they often possess  $\pi$ -bonds that are suitably oriented for controlled transannular reactions, leading perhaps to bicyclo[4.4.0]- and bicyclo[5.3.0]decane derivatives.
3. In designing possible 6 + 4 cycloadditions, all possible competing 4 + 2 processes must be considered.
4. Cope rearrangements of 6 + 4 products are frequently so fast that these products would never be observed in practice.
5. Substituents effects on the rates of 6 + 4 cycloadditions appear to be closely related to those seen for 4 + 2 reactions. In particular, the introduction of electronegative substituents in either the  $6\pi$  or  $4\pi$  reactant can lower activation energies substantially, paralleling the effects seen for “normal” and “inverse electron demand” Diels–Alder reactions.

6. The problems associated with points 3 and 4 above may be overcome in many cases by the judicious introduction of substituents. We suggest that substituted versions of **16**, **18**, **20**, **23**, **25**, **28**, **29**, **31**, **33**, **39**, **40**, and **41** may be prepared by 6 + 4 cycloaddition in the laboratory (see Scheme 13 for examples). We stress again the point made earlier that adding substituents to terminal atoms of the reactants will normally decrease the exothermicity of 6 + 4 cycloadditions and may render them impractical. On the other hand, the introduction of nonterminal substituents that retain conjugation after cycloaddition often has the opposite effect and, in particular, can render Cope rearrangement of the 6 + 4 products unfavorable.

7. Substituted versions of 6 + 4 cycloaddition products **24** and **30** should produce unique further rearrangement products (Scheme 14).

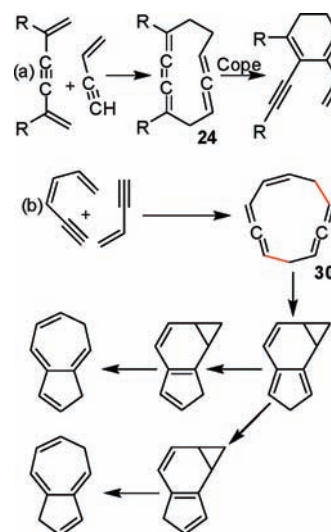
In summary, while 6 + 4 cycloaddition routes to 10-membered ring products are never likely to approach the generality of the Diels–Alder route to cyclohexenes and

**Scheme 13.** Examples of 6 + 4 Cycloadducts Whose Formation May Be Practical<sup>a</sup>



<sup>a</sup>  $\sigma$ -bonds formed in the cycloaddition are shown in red, and activation energies are in kJ mol<sup>-1</sup>. Note that the use of cyano and imide groups as substituents is largely based on computational economy and that related substituents could be used.

**Scheme 14.** Rearrangement Products Predicted To Result for the Formation of (a) **24** and (b) **30**



cyclohexadienes because substituents will always have to be chosen with a view to minimizing competing 4 + 2 reactions and Cope rearrangements, we do suggest that experimental study of some of the possibilities we have uncovered would be interesting and fruitful.

## Theoretical Methods

All DFT calculations were initially performed using Becke's three-parameter exchange functional<sup>38</sup> with the correlation functional of Lee, Yang, and Parr (B3LYP).<sup>39</sup> All species were characterized by full geometry optimization with the standard 6-31G\* basis set. Calculations were performed with the Gaussian 03<sup>40</sup> or Spartan<sup>41</sup> program packages. G3(MP2) calculations<sup>42</sup> were

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(39) Lee, C. T.; Yang, W. T.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789.

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(41) *Spartan '06*; Wavefunction, Inc.: Irvine, CA, 2006.

(42) Curtiss, L. A.; Redfern, P. C.; Raghavachari, K.; Rassolov, V.; Pople, J. A. *J. Chem. Phys.* **1999**, *110*, 4703–4709.

carried out with Gaussian 03 and MOLPRO 2006.<sup>43</sup> Minima and TSs were characterized by analytical frequency calculations. All activation and reaction energies include zero-point corrections. IRC calculations were carried out with Gaussian 03. Cartesian coordinates and SCF energies for all the TSs discussed in this paper are available in the Supporting Information.

The global minimum conformation for many species discussed in this paper cannot be safely predicted by inspection. Monte Carlo Multiple Minimum conformational searches<sup>44,45</sup> were therefore carried out, using the MMFFs force field in MacroModel.<sup>46,47</sup> Where several conformations were found to have similar energies by these methods, these were each submitted to B3LYP/6-31G\* calculation, and the lowest energy conformation from this was selected. No attempt has been made, however, to allow for

conformational mixtures, since the error resulting from ignoring this is likely to be small compared with other errors.

**Acknowledgment.** R.W.A. thanks the University of Bristol for a Senior Research Fellowship. G.C.L.-J. is a Royal Society Wolfson Research Merit Award Holder. J.M.O. acknowledges the Spanish Ministry of Science and Innovation under project MAT2009-14234-C03-02. We also thank Prof. Gunter Helmchen for advice concerning the stereochemical designation of approach geometries in 6 + 4 cycloadditions.

**Supporting Information Available:** Complete refs 40 and 43; total energies and geometries for all the transition states discussed in the paper, together with energies and geometries for selected product conformations; this also includes extended discussion of a number of aspects of this study, including unsubstituted analogues of reactions covered in the paper, problems locating TSs, conformational searches, a possible extension of the exo/endo nomenclature, valley ridge inflection points, and the deficiencies of B3LYP/6-31G\*. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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