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Intermolecular [4+2] Cycloadditions of a Reactive Cyclopentadienone

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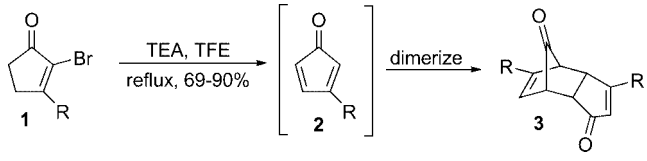
A reactive cyclopentadienone gives Diels–Alder cycloadducts with a variety of dienes in high yield and often with extremely high levels of regio- and stereoselectivity. The high degree of generality of this reaction suggests it will be of use in organic synthesis.

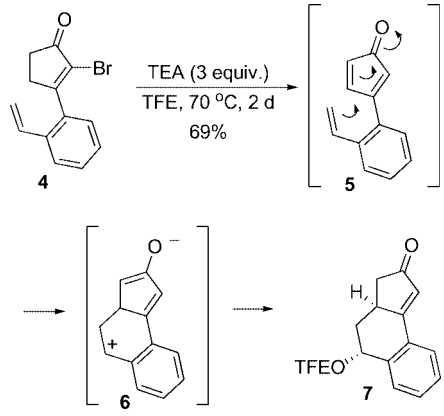
We recently reported the generation of cyclopentadienones from 2-bromocyclopentenones by treatment of the latter with triethylamine in refluxing trifluoroethanol (TFE) (Scheme 1).[1]



Scheme 1. Formation of a cyclopentadienone dimer.

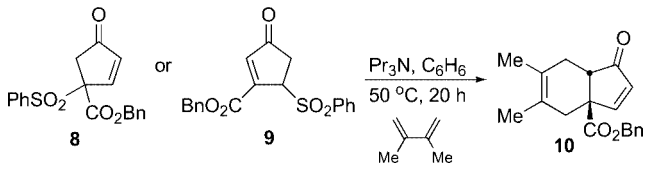
Eager to apply this "new"[2] approach to cyclopentadienones in some fashion, we became generally interested in exploring antiaromatic intermediates as a driving force in organic reactions, a concept we have termed "deantiaromatization". This idea led to our discovery of an electrocyclic reaction of cyclopentadienones illustrated in Scheme 2.[3] In searching for another application of cyclopentadienones, we became very excited by the reports by Gavina[4] and by Fuchs,[5] in which it was shown that a reactive cyclopentadienone could be a competent dienophile in a [4+2] cycloaddition (Diels–Alder) process.

Common knowledge suggests that reactive cyclopentadienones dimerize very rapidly.[6] Indeed, a number of strategies have been developed to combat this problem in the form of syntheses of relatively stable, monomeric cyclopentadienones that are competent dienophiles and dienes in [4+2] cycloaddition reactions.[7] Fuchs's paper presented a small number of intriguing examples that suggested that such special precautions need not be taken. For example, treatment of either **8** or **9** with tripropylamine in benzene at 50 °C in the presence of 5 equiv. of 2,3-dimethylbutadiene



Scheme 2. Electrocyclization of a cyclopentadienone.

afforded **10** in 84% and 71% yield, respectively (Scheme 3). Unlike the corresponding cyclobutadiene,[8] attempts to perform an intramolecular version of this reaction were unsuccessful. To the best of our knowledge, there has been no subsequent or related work on this chemistry. We saw an opportunity to exploit our cyclopentadienone chemistry and further explore the scope of this elegant and mild cyclopentadienone cycloaddition process. We report our preliminary results herein.



Scheme 3. Fuchs's cyclopentadienone cycloaddition.

We began our study simply by attempting to generate a cyclopentadienone from **11**.[9] Of several sets of reaction conditions studied, we found that the treatment of **11** with 2 equiv. of triethylamine in toluene at reflux for 1 h afforded the decarbonylated dimer (DCD), the indanone **14**, in 71%

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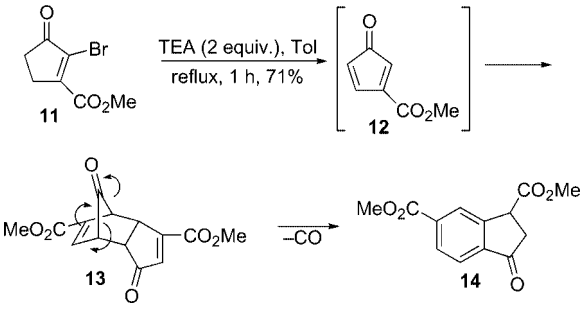
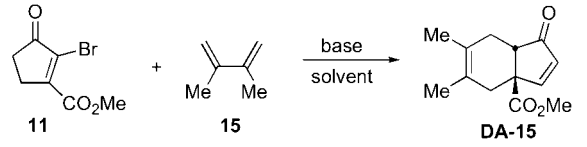
yield.[10] The reaction presumably proceeded through the pathway shown in Scheme 4, in which cyclopentadienone formation was followed by dimerization and decarbonylation to afford the indanone **14**.



Scheme 4. Generation of a cyclopentadienone from **11**.

To evaluate [4+2] cycloadditions of **11**, experiments using 2,3-dimethylbutadiene as a test substrate were conducted. The results are shown in Table 1. We initially looked at several solvents using 5 equiv. of triethylamine (TEA) as base. It appeared that toluene and THF were the most effective. To this point, little effort has been put into varying the concentration, but more than doubling the concentration of the reaction in THF essentially afforded the same yield of cycloadduct. Stronger bases such as DBU proved too potent and apparently destroyed the starting material. The hindered base 2,2,6,6-tetramethylpiperidine (TMP) afforded the product in THF, but the yield was considerably lower than when TEA was used. Given these results, we decided to pursue cycloadditions using TEA as base in toluene or THF as the reaction solvent.

Table 1. Optimization of the reaction between **11** and 2,3-dimethylbutadiene via **12**.[a]



Entry	Base (equiv.)	Solvent	Time (min)	Yield (%)
1	TEA (5)	MeCN	35	22
2	TEA (5)	1.4-dioxane	70	54
3	TEA (5)	[b]	255	22[c]
4	TEA (5)	2-butanone	40	61
5	TEA (5)	acetone	210	22
6	TEA (5)	toluene	90	84
7	TEA (3)	THF	160	73
8	TEA (3)	THF	160	71[d]
9	DBU (3)	toluene	20	[e]
10	DBU (3)	2-butanone	14	[e]
11	TMP (3)	THF	70	43

[a] All reactions were conducted at the reflux temperature of the solvent unless otherwise noted at a concentration of 0.04 M with respect to **11**. [b] 1-Butyl-3-methylimidazolium tetrafluoroborate. [c] Reaction conducted at 85 °C. [d] Reaction conducted at a concentration of 0.1 M. [e] Decomposition of starting material.

In general, the results suggest that the reaction proceeds better in toluene than in THF. It appears that cyclopentadienone generation is more rapid in refluxing toluene, while cycloaddition is competitive with dimerization. The lower yields in THF may reflect starting material or product decomposition over the longer time course of the reaction. For 2,3-dimethylbutadiene, the difference in yield between the two solvents is about 10%. However, as shown in the case of cyclopentadiene, cycloaddition reactions of **11** can proceed well in THF (Table 2, Entry 4). The reaction with cyclohexadiene clearly benefited from a change from THF to toluene (Table 2, Entries 5–6).

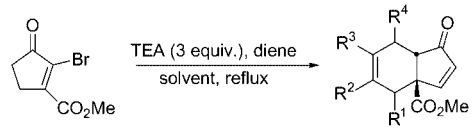
Interestingly, 1,2-dialkylbutadienes react with **11** to afford cycloadducts as single regio- and stereoisomers (Table 2, Entries 7–12). Especially attractive among the examples in Table 2 is that in Entry 12. The product bears the carbocyclic skeleton of a steroid, marking the methodology as a potential entry to this important class of compounds. The stereochemistry of **DA-22** was established by NMR studies, particularly NOESY spectra. The appropriate interactions that led to the stereochemical assignment shown were observed. This suggests an *endo* approach of the diene to the cyclopentadienone and is entirely consistent with other structural data (vide infra).

Results with 1-substituted butadienes were somewhat mixed. Piperylene gave a poor yield of cycloadduct, though the product was a single isomer (Table 2, Entry 13). This result may simply stem from the volatility of the diene. Thus, when 10 equiv. of diene were used and the reaction was conducted in a sealed tube, **DA-23** was obtained in a yield of 71 %, along with 14% of the DCD **14**. Related aryl-substituted systems performed better, affording regiochemically and stereochemically clean products (Table 2, Entries 14 and 16). Interestingly, it appears that 2-substituted dienes can react well with **11** to give cycloadducts, but with virturally no regioselectivity (Table 2, Entry 15). Further studies of this phenomenon are in progress.

The importance of electronic effects on the course of the reaction could be gleaned from studies of other 1-substituted dienes. For example, 1-methoxybutadiene and the corresponding TBS silyl ether gave clean cycloadducts in excellent yield (Table 2, Entries 17–19). However, with compound **29** under essentially the same conditions, only a 30% yield of the Diels–Alder adduct **DA-29** was observed, the major product being the DCD **14** (41%). The lower reactivity of the diene could be circumvented by increasing its concentration. Thus, when 5 equiv. of **29** was used, the yield of the cycloadduct **DA-29** improved to 72% (Table 2, Entry 21). Similar results were realized with compound **30** (Table 2, Entries 22–23). The structure of the cycloadduct **DA-30** was established by X-ray analysis.[11]

Good yields of cycloadducts were obtained with the dienes **31**–**34**. Interestingly, we had some problems in using Danishefsky's diene **31**. The reaction benefited greatly from the inclusion of 20 mol-% of triethylamine hydrobromide. The reasons behind this are not clear, and we are still attempting to improve the cycloaddition process with this diene and understand the effect of additives on the yield. The dienyl sulfide **33** performed very well in the cycloaddition. The structure of the cycloadduct was established by X-ray analysis of the corresponding sulfone, produced in

Table 2. [4+2] Cycloaddtion reactions of cyclopentadienone **12**.



11 **DA-15–34**

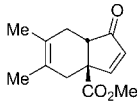
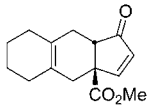
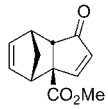
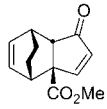
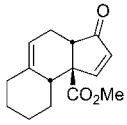
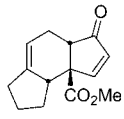
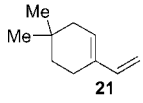
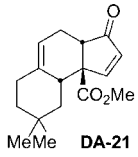
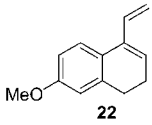
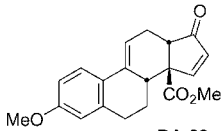
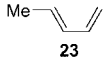
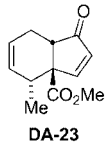
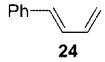
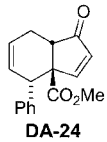
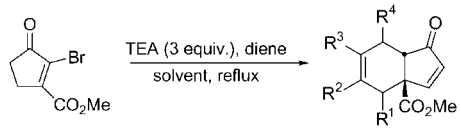
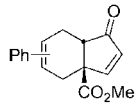
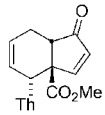
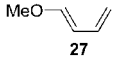
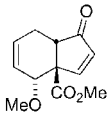
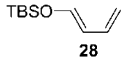
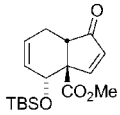
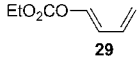
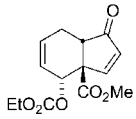
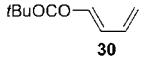
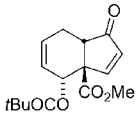
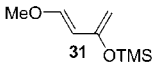
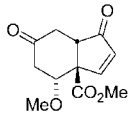
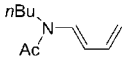
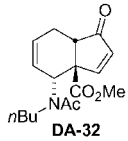
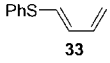
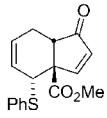
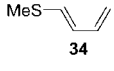
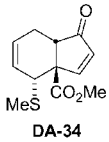
Entry	Diene (equiv.)		Time (h)	Solvent	Product	Yield (%)
1	 **15**	(10)	6	THF	 **DA-15**	73
2	**15**	(10)	1.5	Toluene	**DA-15**	84
3	 **16**	(5)	1.25	Toluene	 **DA-16**	82
4	 **17**	(10)	2.75	THF	 **DA-17**	89
5	 **18**	(3)	4	THF	 **DA-18**	17
6	**18**	(3)	1.5	Toluene	**DA-18**	57
7	 **19**	(3)	4	THF	 **DA-19**	63
8	**19**	(3)	1.5	Toluene	**DA-19**	77
9	 **20**	(3)	3	THF	 **DA-20**	33
10	**20**	(3)	1.5	Toluene	**DA-20**	56
11	 **21**	(3)	1.75	Toluene	 **DA-21**	80
12	 **22**	(2)	1.5	Toluene	 **DA-22**	80
13	 **23**	(5)	1.75	Toluene	 **DA-23**	13[a]
14	 **24**	(4)	1.25	Toluene	 **DA-24**	66

Table 2. *(continued)*.



11 **DA-15–34**

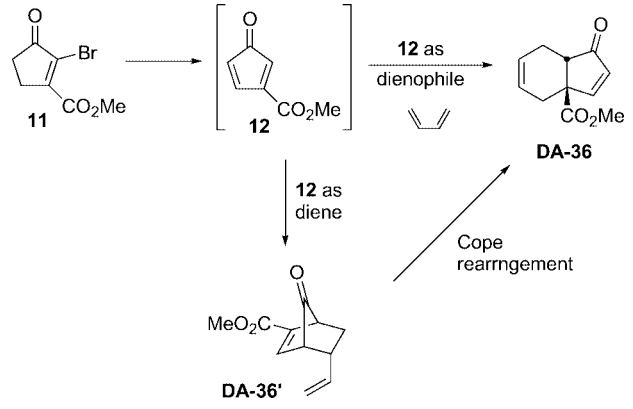
Entry	Diene (equiv.)	Time (h)	Solvent	Product	Yield (%)
15	 **25**	(2)	1.25	Toluene	 **DA-25**	80[b]
16	 **26**	(2)	1.25	Toluene	 **DA-26**	8[c]
17	 **27**	(2)	6	THF	 **DA-27**	52
18	**27**	(2)	2.25	Toluene	**DA-27**	84
19	 **28**	(5)	1.25	Toluene	 **DA-28**	79
20	 **29**	(2)	1.25	Toluene	 **DA-29**	30[d]
21	**29**	(5)	1.75	Toluene	**DA-29**	72
22	 **30**	(2)	1.25	Toluene	 **DA-30**	31[e]
23	**30**	(5)	1.25	Toluene	**DA-30**	61[f]
24	 **31**	(5)	5	Benzene	 **DA-31**	53[g]
25	 **32**	(3)	1.75	Toluene	 **DA-32**	84
26	 **33**	(5)	1.25	Toluene	 **DA-33**	84
27	 **34**	(4)	1.25	Toluene	 **DA-34**	69

[a] Plus 26% of **14**. [b] The ratio of regioisomers was 1:1 based on ^{1}H NMR analysis. [c] Th = 2-thienyl. [d] Plus 41% of **11**. [e] Plus 35% of **11**. [f] Plus 10% of **11**. [g] This reaction was run in the presence of 20 mol-% of triethylamine hydrobromide.

74% yield by oxidation of **DA-33** with *m*CPBA.[11] The stereostructures of other cycloadducts, if not secured with NOE data, were assigned based on the X-ray data we obtained. Thus far, all data appear to be consistent with our assignments.

How does the reaction really proceed? We attempted to perform the reaction without base. Cycloaddition between **11** and the dienes **15** or **31** in the absence of base in refluxing THF or benzene resulted in the recovery of starting material (41–75%) with no evidence for the formation of a cycloadduct of any kind. This fact, along with the formation of **14** in the presence of base but absence of diene, strongly suggests the formation of **12** as the reactive intermediate in these reactions.

Diels–Alder reactions between two dienes are interesting in that one can ask which diene is the 2π component (dienophile) and which is the 4π component (diene). Recent calculations suggest that both dienes can serve this function simultaneously resulting in a single transition state that bifurcates to produce two different products which are separated by a Cope rearrangement.[12] This is illustrated in Scheme 5 with butadiene. We carried out the reaction between **28** and **11** at room temperature (toluene, 7 d) in the hope of isolating a structure like **DA-36′**. Only the cycloadduct **DA-28** was formed in 53% yield. We are continuing to study the mechanistic aspects of this reaction.



Scheme 5. Possible paths for the formation of cycloadducts.

In summary, we have shown that a reactive cyclopentadienone can be an effective partner in highly regioselective and stereoselective [4+2] cycloadditions with certain dienes. Along with the work by Fuchs, this demonstrates that a variety of cyclopentadienone precursors will generally give rise to cyclopentadienones under mild conditions that can participate in these and related cycloaddition reactions. We are presently exploring these possibilities and the application of the methodology to total synthesis. Results will be reported in due course.

Supporting Information (see footnote on the first page of this article): Experimental procedures for the cycloaddition reaction, characterization data for the cycloadducts and copies of proton and carbon NMR spectra.

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[9] Details of the synthesis of this compound will be published elsewhere.
[10] The indanone was formed as a 10:1 mixture of isomers according to the ^{1}H NMR spectrum of the crude reaction mixture. We believe the minor isomer is a constitutional isomer arising from a highly, but not completely, regioselective cycloaddition.
[11] CCDC-297302 (**DA-30**), and -297303 (sulfone of **DA-33**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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