New Generation and Intramolecular Diels-Alder Reaction of Isobenzofurans: An Efficient Furan Ring-Transfer Reaction and a Synthetic Entry into the Polycyclic Ring Systems

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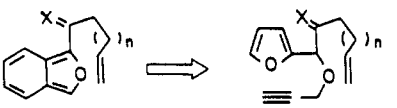
The generation and intramolecular Diels-Alder reaction of isobenzofurans **3-6** have been investigated. The precursors **15-22** of isobenzofurans were prepared in one pot from the furfuryl propargyl ethers **7-10** by treating with *t*-BuOK in *t*-BuOH (83 °C) via the intramolecular Diels-Alder reaction of initially formed allene intermediates and spontaneous ring opening of the adducts (furan ring-transfer reactions). Treatment of **15-22** with a catalytic amount of camphorsulfonic acid (CSA) in refluxing toluene resulted in generation of the corresponding isobenzofuran intermediates **3-6**. The isobenzofurans carrying a 1,3-dithiane moiety on the connecting carbon chain (**3** and **4**) smoothly underwent the intramolecular Diels-Alder reaction to give the cycloadducts **25, 26** and **28, 30**. However, the similar reaction of isobenzofurans without 1,3-dithiane moiety (**5** and **6**) only led to polymeric substances, whereas the formation of **5** and **6** was confirmed by the intermolecular Diels-Alder reaction with dimethyl acetylenedicarboxylate (DMAD). The structure-reactivity relationship in these isobenzofurans was discussed on the basis of the results of competitive inter- vs. intramolecular cycloaddition.

Introduction

The intramolecular Diels-Alder reaction has become one of the most useful synthetic protocols in modern organic synthesis.[1] The reaction has been applied to the syntheses of a number of interesting polycyclic ring systems as well as natural products.[2] Previously, we found that the allene unit is a versatile synthon as the dienophile in the intramolecular Diels-Alder reaction due to the absence of unfavorable nonbonded interactions in the transition state.[3-6] From this point of view, we have developed a new method for the transformation of furans **1** into fused furans **2** (furan ring-transfer (FRT) reaction) via the intramolecular Diels-Alder reaction of the allenyl furfuryl ether followed by base-catalyzed ring opening of the resulting adduct as shown in Scheme I.[4] Furthermore, the resulting fused furans **2** proved to be useful precursors of the synthetically versatile isobenzofurans.[7]

While intermolecular Diels-Alder reactions of isobenzofurans have been well investigated, the intramolecular counterparts have received less attention.[8] On the basis of the combined FRT reaction and acid-catalyzed dehydration, we have explored a new and efficient generation of variously functionalized isobenzofurans which may undergo intramolecular Diels-Alder reaction, as outlined in Scheme II. This paper describes the full details of the work including the previously undisclosed structure-reactivity relationship in the cycloaddition reactions of isobenzofurans.[4]

Chart I



3	n= 1, X= $S(CH_2)_3S$	**7**
4	n= 2, X= $S(CH_2)_3S$	**8**
5	n= 1, X= H, H	**9**
6	n= 2, X= H, H	**10**

Results and Discussion

Preparation of Propargyl Ethers 7-10. For the study of the intramolecular Diels-Alder reaction of isobenzofurans, it is required to synthesize some isobenzofuran derivatives bearing an olefin as the intramolecular dienophile through a flexible carbon chain like **3-6** (Chart I). For this purpose, the corresponding propargyl ethers **7-10** were considered to be ideal precursors on the basis of the retrosynthetic analysis of the FRT reaction.[4] Thus, syntheses of requisite **7-10** were carried out by the routes as shown in Schemes III and IV. Compounds bearing the 1,3-dithiane moiety (**7** and **8**) were readily prepared by the nucleophilic addition of carbanions[9] derived from the appropriate dithiane derivatives to furfural and the successive propargylation of the resulting furfuryl alcohols (**11** and **12**) (Scheme III). Ether **9** was obtained by a one-pot reaction of 2-furyllithium[10] and 5-hexenal followed by the propargylation, while its homologue **10** was prepared via alkylation of furfural (Scheme IV). The structures of these compounds were confirmed by the spectroscopic data (given in the supplementary material).

Furan Ring-Transfer Reaction. Using our previously described procedure,[4] the propargyl ethers **7-10** were subjected to the FRT reactions. The results are summarized in Table I. For example, treatment of **7** with 2 equiv of potassium *tert*-butoxide in refluxing *tert*-butyl alcohol

(1) Reviews: (a) Ciganek, E. *Organic Reactions*; Wiley: New York, 1984; Vol. 32. (b) Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63. (c) Oppolzer, W. *Angew. Chem., Int. Ed. Eng.* **1977**, *16*, 10. (d) Funk, R. L.; Vollhardt, K. P. C. *Chem. Soc. Rev.* **1980**, *9*, 41.

(2) A few recent examples: (a) Funk, R. L.; Bolton, G. L. *J. Am. Chem. Soc.* **1986**, *108*, 4655. (b) Kozikowski, A. P.; Jung, S. *Tetrahedron Lett.* **1986**, *27*, 3227. (c) Moursounidis, J.; Wege, D. *Tetrahedron Lett.* **1986**, *27*, 3045. (d) Grootaert, W. M.; De Clercq, P. J. *Tetrahedron Lett.* **1986**, *27*, 1731. (e) Magnus, P.; Walker, C.; Jenkins, P. R.; Menear, K. A. *Tetrahedron Lett.* **1986**, *27*, 651. (f) Thomas, E. J.; Whitehead, J. W. F. *J. Chem. Soc., Chem. Commun.* **1986**, 724. (g) Hecker, S. J.; Heathcock, C. H. *J. Org. Chem.* **1985**, *50*, 5159. (h) Nicolaou, K. C.; Papahatjis, D. P.; Claremon, D. A.; Magolda, R. L.; Dolle, R. E. *J. Org. Chem.* **1985**, *50*, 1440.

(3) Hayakawa, K.; Yodo, M.; Ohsuki, S.; Kanematsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 6735.

(4) Hayakawa, K.; Yamaguchi, Y.; Kanematsu, K. *Tetrahedron Lett.* **1985**, *26*, 2689.

(5) Hayakawa, K.; Ohsuki, S.; Kanematsu, K. *Tetrahedron Lett.* **1986**, *27*, 947.

(6) Hayakawa, K.; Yasukouchi, T.; Kanematsu, K. *Tetrahedron Lett.* **1986**, *27*, 1837.

(7) Reviews: (a) Wiersum, W. *Aldrichimica Acta* **1981**, *14*, 53. (b) Friedrichsen, W. *Adv. Heterocycl. Chem.* **1980**, *26*, 135.

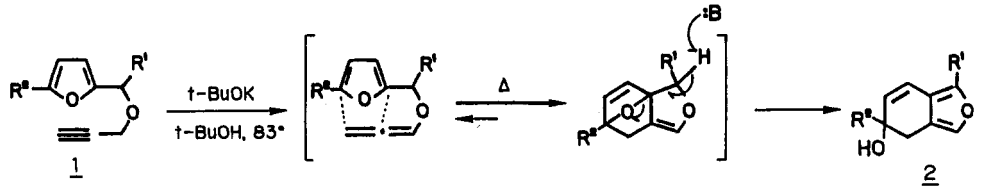
(8) (a) Keay, B. A.; Rodrigo, R. *J. Am. Chem. Soc.* **1982**, *104*, 4725. (b) Halverson, A.; Keehn, P. A. *J. Am. Chem. Soc.* **1982**, *104*, 6125. (c) Friedrichsen, W.; Koning, B.-M.; Hildebrandt, K.; Debacrdemaeker, T. *Heterocycles* **1986**, *24*, 297.

(9) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231.

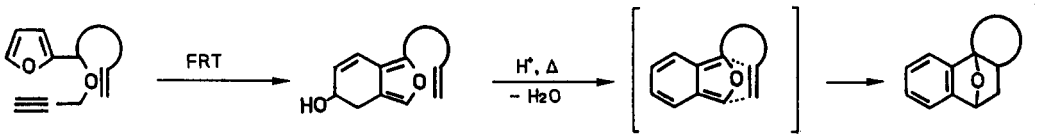
(10) Chadwick, D. J.; Willbe, C. J. *J. Chem. Soc., Perkin Trans. 1* **1977**, 887.

0022-3263/87/1952-2040$01.50/0

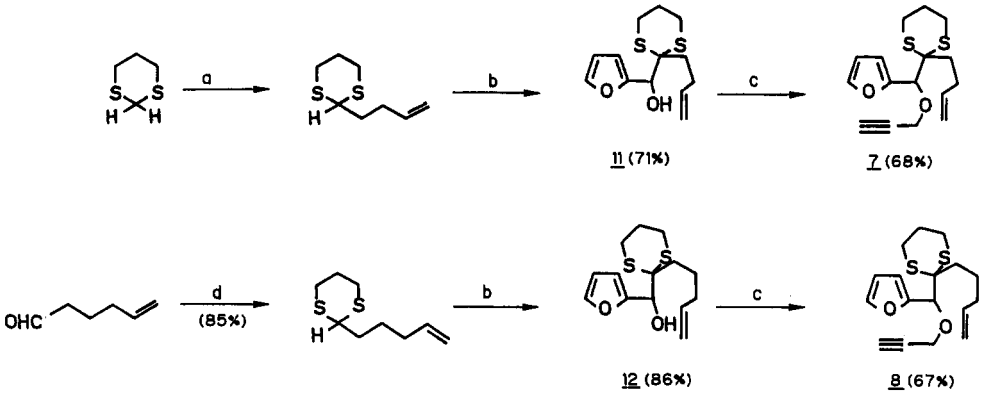
Scheme I



Scheme II

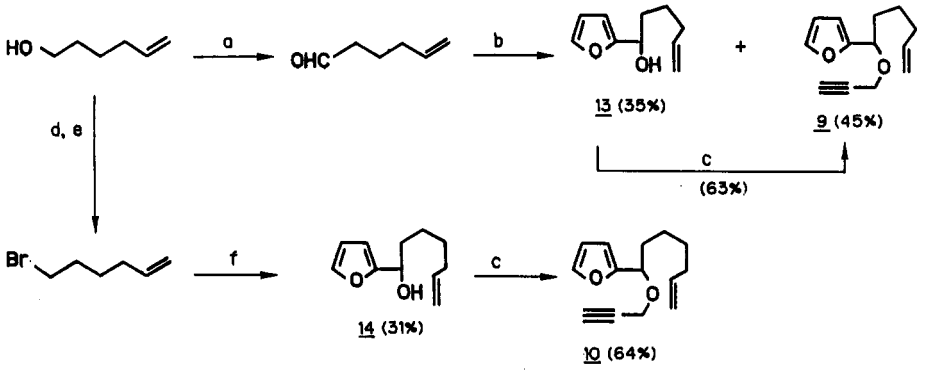


Scheme III[a]



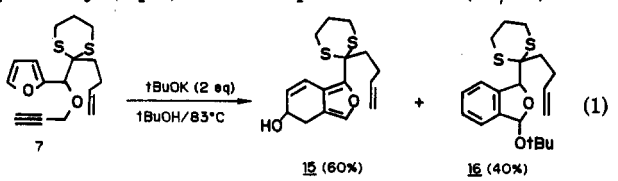
[a] Reaction conditions: (a) *n*-BuLi, THF, then $Br(CH_2)_2CHCH_2$; (b) *n*-BuLi, THF, then furfural; (c) *n*-BuLi, THF; HMPA, then $BrCH_2CCH$; (d) $HS(CH_2)_3SH$, $Mg(OTf)_2$, CH_2Cl_2.

Scheme IV[a]



[a] Reaction condition: (a) $(COCl)_2$, Me_2SO, Et_3N, CH_2Cl_2; (b) 2-furyllithium, THF; HMPA, then $BrCH_2CCH$; (c) *n*-BuLi, THF; HMPA, then $BrCH_2CCH$; (d) MsCl, Et_3N, CH_2Cl_2; (e) LiBr, HMPA; (f) Mg, THF, then furfural.

(83 °C; 1 h) produced **15** and **16** in 60% and 40% yields, respectively (eq 1).[11] The product ratio (**15**/**16**) was



(1)

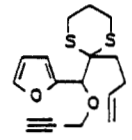
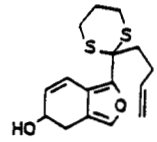
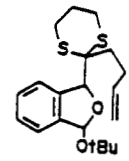
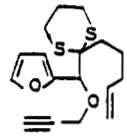
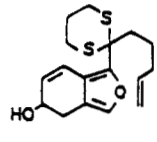
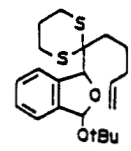
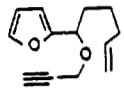
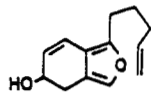
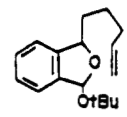
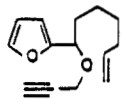
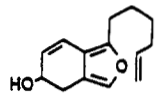
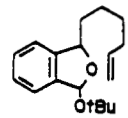
changeable depending upon the amount of the base used, and more **15** was formed as more base was employed. As Table I shows, propargyl ethers **8**–**10** similarly underwent the FRT reactions in high efficiency to give two products in varying ratios depending upon the reaction conditions.

Due to the large difference in the polarity of these compounds (e.g., **15** and **16**), each product was easily isolated by column chromatography on silica gel impregnated with 5% K_2CO_3.[18] The alcoholic structure of the more polar **15** (M^+ 308) was apparent from the IR (3380 cm^{-1}) and ^1H NMR spectrum [δ 1.64 (1 H, s, D_2O exchangeable)], while the less polar **16** (M^+ 364) was characterized by a sharp singlet at δ 1.39 attributable to a *tert*-BuO group.

Since no interconversion between **15** and **16** was observed under the reaction conditions, these products might arise independently via different pathways as illustrated in Scheme V. The base treatment of **7** initially causes isomerization to the allene intermediate **23**,[12] which

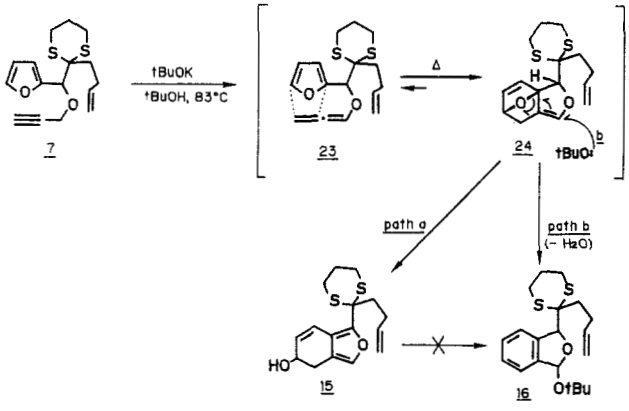
(11) In careful reexamination of reactions of the previously reported substrates (i.e. 1),[4] we observed that the phthalan-type products were also formed (ca. 30%) in the case of alkylated derivatives (1, R^1 = alkyl), while the reaction of 1 (R^1 = Ar or H) gave almost exclusively alcoholic products (>95%) and only a trace amount (<3%) of phthalan products.

Table I. Furan Ring-Transfer Reaction[a]

entry	substrate	t-BuOK, equiv	product (yield,[b] %)	
a				
	7		15	16
		2	(60)	(40)
		10	(72)	(19)
b				
	8		17	18
		2	(66)	(33)
		10	(80)	(17)
		20	(91)	(9)
c				
	9		19	20
		10	(55)	(33)
		20	(76)	(19)
d				
	10		21	22
		2	(52)	(48)
		10	(63)	(33)

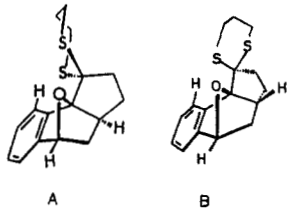
[a] All reactions were carried out in t-BuOH at 83 °C utilizing the given amount of t-BuOK until the starting materials were completely consumed (1–2 h). [b] Isolated yield.

Scheme V



smoothly undergoes intramolecular Diels–Alder reaction to give cycloadduct **24**. For the ring opening of the strained oxabicyclo[2.2.1]hexene ring system of **24**, there might be two competitive pathways under such basic reaction conditions: the base-catalyzed deprotonative C–O bond cleavage (β-elimination) may afford allyl alcohol **15** (path a) (cf. Scheme I), whereas the S_N2'-like C–O bond cleavage initiated by the nucleophilic addition of *tert*-butoxide anion and the successive dehydrative aromatization may lead to *tert*-butoxyphthalane **16** (path b). While the path

Chart II



a seems to be the more favorable process in the parent systems (i.e., **1**, R^1 = H),[11] the steric hindrance caused by the substituent on the chain in **7–10** might result in the concomitant occurrence of path b.

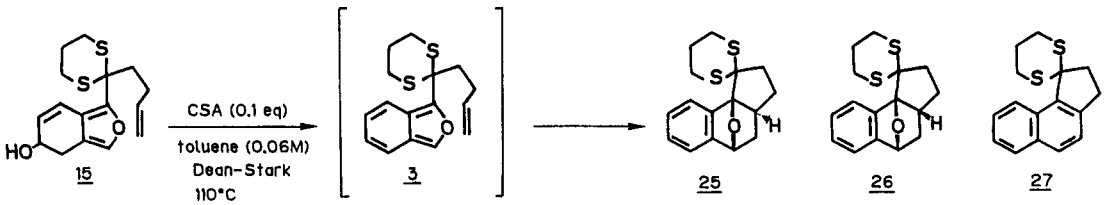
Intramolecular Diels–Alder Reaction of Isobenzofuran. With **15–22** in hand, we next turned our attention to the intramolecular Diels–Alder reaction of isobenzofurans.[13] Brief heating of **15** in refluxing toluene (0.07 M, 3 min) in the presence of 0.1 equiv of camphorsulfonic acid (CSA) using a Dean–Stark apparatus[14] resulted in formation of a 4:1 mixture of cycloadducts **25** (exo) and **26** (endo) in 99% combined yields (Scheme VI). Each isomer was isolated by a silica gel column chromatography (**25** is more polar than **26**). While **25** was fairly stable, **26** grad-

(12) Brandsma, L.; Verkruijsse, H. D. *Synthesis of Acetylenes, Allenes, and Cumulenes*; Elsevier Scientific: New York, 1981; pp 87–114.

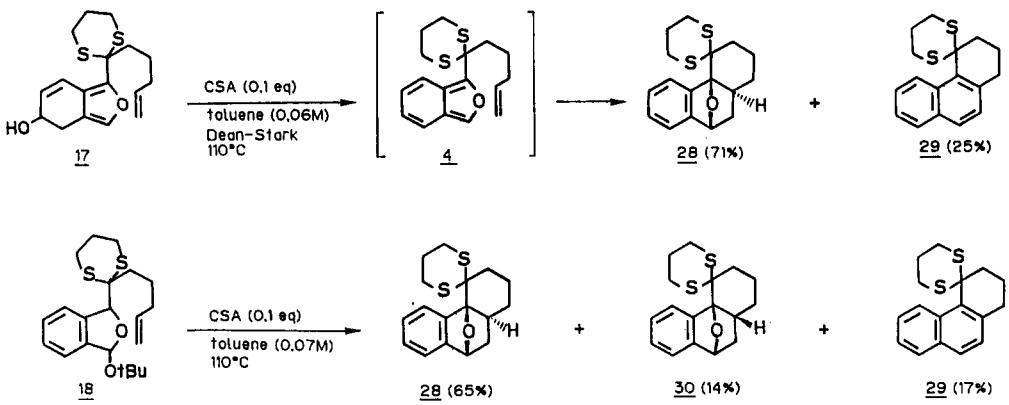
(13) 1-*tert*-Butoxyphthalans are known to be good precursors of isobenzofurans. See: (a) Naito, K.; Rickborn, B. *J. Org. Chem.* **1980**, *45*, 4061. (b) Moss, R. J.; Rickborn, B. *J. Org. Chem.* **1982**, *47*, 4011.

(14) An attempt for the intramolecular cycloaddition under the previously reported reaction condition (1 equiv of *p*-TsOH, THF, 25 °C)[4] resulted in a complex mixture of many byproducts.

Scheme VI

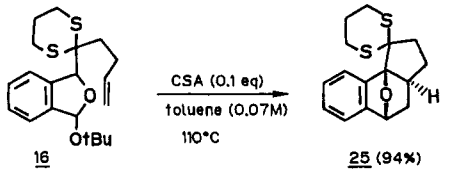


Scheme VII



ually decomposed on standing to give the naphthalene derivative **27**. The stereochemical assignment of these products was based on the ^1H NMR spectral comparison. Remarkably, the exo adduct **25** showed the H-4 signal at the lower field compared with that of endo **26** ($\Delta\delta = 0.28$). An examination of the molecular model suggests that this low-field shift may be attributed to the anisotropic effect of the sulfur atoms in the 1,3-dithiane ring, which are located to flank the H-4 in *exo*-**25** (Chart II). Furthermore, the observed instability of **26** assigned the endo adduct is compatible with the fact that *cis*-bicyclo[3.3.0]octane is more stable than that of trans isomer.[15]

On the other hand, treatment of **16** with 0.1 equiv of CSA in refluxing toluene (0.06 M, 3 min) gave rise to a single stereoisomer **25** in 94% (eq 2).



(2)

Similarly, compounds **17** and **18** underwent a smooth intramolecular cycloaddition via isobenzofuran intermediate as shown in Scheme VII. While the reaction of **18** gave both *exo*-**28** and *endo*-**30** together with naphthalene derivatives **29**, reaction of **17** afforded no *endo*-**30**. This might be attributed to the instability of **30** under these reaction conditions. Actually, the control experiment showed that dehydration of **30** to **29** occurred more easily than that of **28**. The structural assignments of these products were made on the basis of their spectral comparison with those of **25–27**. It should be noted that all these reactions proceeded in extraordinary short time (3 min) and in high yield.

In sharp contrast, none of **19–22**, which have no 1,3-dithiane ring on the side chain, underwent such a smooth intramolecular cycloaddition. The similar acid treatment of these compounds caused only a rapid decomposition (polymerization) probably via the isobenzofuran intermediates (vide infra). These results suggested that the intramolecular Diels–Alder reaction of isobenzofurans are strongly affected by the substituents on the side chain linking the isobenzofuran and dienophile as generally established in the intramolecular cycloaddition reactions.[16]

Competitive Intermolecular and Intramolecular Diels–Alder Reactions. In order to substantiate the generation of isobenzofurans and to clarify their tendencies toward intermolecular vs. intramolecular cycloaddition,[17] we have attempted the acid-catalyzed reaction of **15–22** in the presence of equal amount of dimethyl acetylenedicarboxylate (DMAD) as the intermolecular trapping agent: i.e., competitive intermolecular vs. intramolecular Diels–Alder reaction (Table II). As Table II shows, compounds **19–22** with no substituent on the side chain exclusively underwent the intermolecular cycloaddition with DMAD to give the Diels–Alder adducts **33** and **34**, while the 1,3-dithiane derivatives **15–18** afforded both intermolecular (**31** and **32**) and intramolecular cycloadducts (**25** and **28**) with the latter in favor. From these results, the following criteria may be drawn. (i) Isobenzofurans (**3–6**) can readily be generated in the acid-catalyzed reaction of **15–22**. (ii) The 1,3-dithiane on the side chain is necessarily important for the intramolecular cycloaddition, presumably in order to cause the larger population of the favorable conformation for the diene–dienophile overlap in the transition state.[16e] (iii) The intramolecular cycloaddition through the three-carbon chain (five-membered ring formation; **25**) seems to be easier than that through the four-carbon chain (six-membered ring formation; **28**).

In conclusion, the intramolecular Diels–Alder reaction of isobenzofurans via the FRT reaction has been demonstrated. We believe that this methodology provides an efficient means for gaining access to multiply fused ring systems.

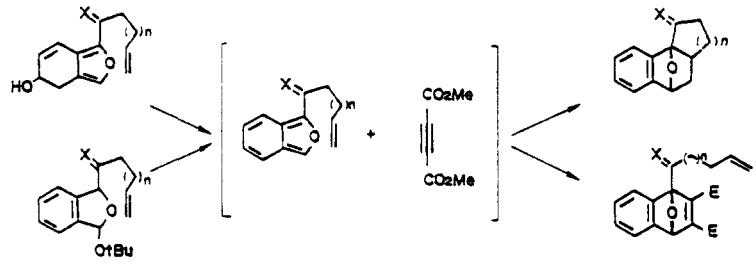
(15) Dale, J. *Stereochemistry and Conformational Analysis*; Universitetsforlaget: Oslo, 1978; Chapter VI.

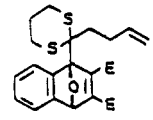
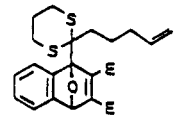
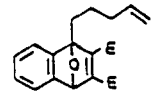
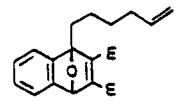
(16) (a) Parker, K. A.; Adamchuk, M. R. *Tetrahedron Lett.* **1978**, 1689. (b) Boeckman, R. K., Jr.; Ko, S. S. *J. Am. Chem. Soc.* **1982**, *104*, 1033. (c) Sternbach, D. D.; Rossana, D. M. *Tetrahedron Lett.* **1982**, *23*, 303. (d) Jung, M. E.; Street, L. J. *J. Am. Chem. Soc.* **1984**, *106*, 8327. (e) Sternbach, D. D.; Rossana, D. M.; Onan, K. D. *Tetrahedron Lett.* **1984**, *26*, 591.

(17) Funk, R. L.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1980**, *102*, 5245.

(18) The column chromatography on silica gel without impregnation of K_2CO_3 resulted in a substantial decomposition of alcoholic products (e.g., **15**).

Table II. The Competitive Intermolecular and Intramolecular Diels–Alder Reaction



entry	substrate	reaction condition[a]	intermolecular[b] adduct (yield,[c] %)	intramolecular adduct (yield,[c] %)
				
			31	**25**
1	**15**	A	(8)	(71)
2	**16**	B	(9)	(77)
				
			32	**28**
3	**17**	A	(16)	(44)
4	**18**	B	(26)	(55)
				
			33	
5	**19**	A	(59)	
6	**20**	B	(38)	
				
			34	
7	**21**	A	(66)	
8	**22**	B	(26)	

[a] All reactions were carried out in refluxing toluene (110 °C) in the presence of 1 equiv of DMAD: condition A, with a Dean–Stark apparatus; condition B, without a Dean–Stark apparatus. [b] E = COOMe. [c] Isolated yield.

Experimental Section

General. The melting points were measured with Yanagimoto micro melting point apparatus and are uncorrected. The ^1H NMR spectra were taken with a JEOL PS-100 or Hitachi R-600 spectrometer with tetramethylsilane as an internal standard; chemical shifts are expressed in δ values. The ^{13}C NMR spectra were determined with a JEOL PS-100. Mass spectra were determined on a JEOL-D300 equipped with a JMA 3100/3500 at an ionization voltage of 70 eV. Elemental analyses were performed on Yanagimoto MT2 CHN recorder. For thin-layer chromatographic (TLC) analyses, Merck precoated TLC plates (Kieselgel 60 F_{254}, 0.2 mm) were used, and column chromatography was done by using Merck Kieselgel 60 (70–200 mesh) as the stationary phase.

All reactions were carried out under atmospheres of dry argon or nitrogen. All solvents were purified before use: ether and THF were distilled from sodium benzophenone ketyl; CH_2Cl_2 and Me_2SO were distilled from CaH_2; toluene and *t*-BuOH were distilled from sodium metal. *t*-BuOK was purified by sublimation before use.

Preparation of Propargyl Ethers 7–10. Experimental details for the preparation of propargyl ethers **7–10** (Schemes III and IV) and their spectral data are given in the supplementary material.

General Procedure for the FRT Reactions of Propargyl Ethers 7–10. The reaction of **7** is described as an illustrative case. To 1.82 g (16.6 mmol) of *t*-BuOK dissolved in 20 mL of *t*-BuOH at 83 °C was added a solution of propargyl ether **7** (500 mg, 1.62 mmol) in 5 mL of *t*-BuOH. After the addition was complete, the mixture was refluxed for 1 h. After cooling, the resulting mixture was poured into 60 mL of water and extracted with 3 × 60 mL of ether. The combined extracts were washed with 50 mL of brine and dried over Na_2SO_4/K_2CO_3 (1/1). The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (10 g of silica gel impregnated with 5% K_2CO_3, hexane/EtOAc, 5/1–2/1 gradient elution) to give 109 mg (19%) of **16** and 359 mg (72%) of **15** in the order of elution.

1-[2-(3-Butenyl)-1,3-dithian-2-yl]-4,5-dihydroisobenzofuran-5-ol (15): colorless oil; R_f 0.06 (hexane/EtOAc = 5/1); IR (neat) 3380, 3050, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.23–7.20 (m, 1 H), 7.15 (d, J = 10 Hz, 1 H), 5.93 (dd, J = 10, 4 Hz, 1 H), 5.70–5.35 (m, 1 H), 5.08–4.79 (m, 2 H), 4.70–4.35 (m, 1 H), 2.92–2.66 (m, 4 H), 2.50–1.64 (m, 8 H), 1.64 (br s, D_2O exchange, 1 H); mass spectrum, m/e 308 (M^+).

3-[2-(3-Butenyl)-1,3-dithian-2-yl]-1-*tert*-butoxy-1,3-dihydroisobenzofuran (16): colorless oil; R_f 0.46 (hexane/EtOAc = 5/1); IR (neat) 3050, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.89–7.64 (m, 1 H), 7.50–7.10 (m, 3 H), 6.52 (d, J = 2 Hz, 1 H), 5.68 (d, J = 2 Hz, 1 H), 6.12–5.49 (m, 1 H), 5.15–4.82 (m, 2 H), 1.39 (s, 9 H), 3.00–1.22 (m, 10 H); mass spectrum, m/e 364 (M^+).

Similar reaction of **8** (100 mg, 0.31 mmol) using of 348 mg (3.1 mmol) of *t*-BuOK followed by silica gel chromatography afforded **18** (20 mg, 17%) and **17** (80 mg, 80%).

1-[2-(4-Pentenyl)-1,3-dithian-2-yl]-4,5-dihydroisobenzofuran-5-ol (17): colorless oil; R_f 0.08 (hexane/EtOAc = 5/1); IR (neat) 3370, 3070, 1640, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.24–7.21 (m, 1 H), 7.16 (d, J = 10 Hz, 1 H), 5.92 (dd, J = 10, 4 Hz, 1 H), 6.07–5.43 (m, 1 H), 5.13–4.80 (m, 2 H), 4.51 (dt, J = 6, 4 Hz, 1 H), 2.82 (dm, J = 6 Hz, 2 H), 2.86–2.67 (m, 4 H), 2.22–1.26 (m, 9 H).

1-*tert*-Butoxy-3-[2-(4-pentenyl)-1,3-dithian-2-yl]-1,3-dihydroisobenzofuran (18): colorless oil; R_f 0.52 (hexane/EtOAc = 5/1); IR (neat) 3070, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.82–7.23 (m, 4 H), 6.50 (d, J = 2.5 Hz, 1 H), 6.08–5.43 (m, 1 H), 5.67 (d, J = 2.5 Hz, 1 H), 5.15–4.80 (m, 2 H), 2.98–2.69 (m, 4 H), 2.21–1.54 (m, 8 H), 1.38 (s, 9 H); mass spectrum, m/e 378 (M^+), 304 (M – t-BuOH).

Reaction of **9** (200 mg, 0.98 mmol) using t-BuOK (1.099 g, 9.8 mmol) and similar workup gave **20** (79 mg, 33%) and **19** (109 mg, 55%).

1-(4-Pentenyl)-4,5-dihydroisobenzofuran-5-ol (19): colorless oil; R_f 0.11 (hexane/EtOAc = 5/1); IR (neat) 3330, 3070, 1640, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.07–7.02 (m, 1 H), 6.44 (d, J = 9 Hz, 1 H), 5.81 (dd, J = 9, 3.5 Hz, 1 H), 5.50–5.17 (m, 1 H), 5.17–4.83 (m, 2 H), 4.47 (dt, J = 6, 3.5 Hz, 1 H), 2.76 (dm, J = 6 Hz, 2 H), 2.21 (br s, D_2O exchange, 1 H), 2.22–1.51 (m, 6 H).

1-*tert*-Butoxy-3-(4-pentenyl)-1,3-dihydroisobenzofuran (20): colorless oil; R_f 0.54 (hexane/EtOAc = 5/1); IR (neat) 3070, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.31–7.21 (m, 4 H), 6.36 (s, 1 H), 6.08–5.52 (m, 1 H), 5.18–4.79 (m, 3 H), 2.26–1.57 (m, 6 H), 1.36 (s, 9 H); mass spectrum, m/e 187 (M – t-Bu).

Reaction of **10** (100 mg, 0.46 mmol) using t-BuOK (514 mg, 4.6 mmol) afforded **22** (40 mg, 33%) and **21** (63 mg, 63%).

1-(5-Hexenyl)-4,5-dihydroisobenzofuran-5-ol (21): colorless oil; R_f 0.06 (hexane/EtOAc = 5/1); IR (neat) 3350, 3080, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.06–7.03 (m, 1 H), 6.44 (d, J = 9.5 Hz, 1 H), 5.81 (dd, J = 9.5, 3.5 Hz, 1 H), 6.05–5.30 (m, 1 H), 5.15–4.81 (m, 2 H), 4.46 (dt, J = 5.5, 3.5 Hz, 1 H), 2.77 (dm, J = 5.5 Hz, 2 H), 2.61 (t, J = 6.5 Hz, 2 H), 2.23–1.26 (m, 7 H).

1-*tert*-Butoxy-3-(5-hexenyl)-1,3-dihydroisobenzofuran (22): colorless oil; R_f 0.47 (hexane/EtOAc = 5/1); IR (neat) 3080, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.43–7.24 (m, 4 H), 6.37–6.28 (m, 1 H), 5.91–5.58 (m, 1 H), 5.11–4.82 (m, 3 H), 1.39 (s, 9 H), 2.21–1.26 (m, 8 H).

General Procedure for the Intramolecular Diels–Alder Reaction of Isobenzofurans Generated from Alcohols 15 and 17. The reaction of **15** is described as an illustrative case. To 336 mg (1.09 mmol) of **15** dissolved in 16 mL of toluene at 110 °C was added a solution of CSA (30 mg, 0.11 mmol) in 2 mL of toluene. After the mixture was refluxed with azeotropic separation of water by using a Dean–Stark apparatus for 3 min, solid K_2CO_3 (ca. 50 mg) was added, and the mixture was cooled to room temperature. Ether (100 mL) was added, and the mixture was washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure. Silica gel chromatography of the residual mixture using 10/1 hexane/EtOAc as eluent yielded 61 mg (19%) of **26** [R_f 0.4 (hexane/EtOAc = 5/1)] and 252 mg (80%) of **25** [R_f 0.3).

***trans*-1,2,3,4-Tetrahydro-1,4-epoxy-1,2-propanonaphthalen-11-one Trimethylene Dithioketal (25)**: colorless crystal: mp 131.5–133.0 °C; IR ($CHCl_3$) 2950, 2920, 2870, 1450, 1410, 1260, 1030, 980, 940, 920 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 8.02 (dd, J = 6, 2 Hz, 1 H), 7.22–7.12 (m, 3 H), 5.38 (d, J = 4.5 Hz, 1 H), 3.25–1.55 (m, 13 H); ^{13}C NMR ($CDCl_3$) δ 147.0 (s), 142.3 (s), 126.3 (d), 126.2 (d), 121.0 (d), 119.1 (d), 100.2 (s), 78.7 (d), 57.9 (s), 43.2 (d), 40.8 (t), 38.8 (t), 29.3 (t), 27.1 (t), 26.9 (t), 25.7 (t); mass spectrum, m/e 290 (M^+), 184 (M – $S(CH_2)_3S$), 106 (M – 184). Anal. Calcd for $C_{16}H_{18}OS_2$: C, 66.16; H, 6.25. Found: C, 66.06; H, 6.20.

***cis*-1,2,3,4-Tetrahydro-1,4-epoxy-1,2-propanonaphthalen-11-one Trimethylene Dithioketal (26)**: colorless crystal; mp 168.0–169.0 °C; IR ($CDCl_3$) 2980, 2940, 2910, 1450, 1300, 1260, 1045, 1015, 970, 930 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.74 (dm, J = 6 Hz, 1 H), 7.58–7.14 (m, 3 H), 4.78 (d, J = 4 Hz, 1 H), 3.57–1.53 (m, 13 H); mass spectrum, m/e 290 (M^+). Anal. Calcd for $C_{16}H_{18}OS_2$: C, 66.16; H, 6.25. Found: C, 65.93; H, 6.21.

Similar reaction of **17** (113 mg, 0.35 mmol) using CSA (8 mg, 0.04 mmol) followed by silica gel chromatography afforded 76 mg (71%) of **28** [R_f 0.25 (hexane/EtOAc = 10/1)] and 16 mg (16%) of **29** (R_f 0.44).

***trans*-1,2,3,4,4a,9,10,10a-Octahydro-4a,9-epoxyphenanthren-4-one Trimethylene Dithioketal (28)**: colorless crystal; mp 150.0–150.5 °C; R_f 0.25 (hexane/EtOAc = 10/1); IR ($CHCl_3$) 2995, 2920, 2850, 1450, 1435, 1260, 970, 955 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 8.52 (dd, J = 5.5, 2.5 Hz, 1 H), 7.20–7.11 (m, 3 H), 5.33 (d, J = 5 Hz, 1 H), 3.19–3.06 (m, 2 H), 2.75–2.60 (m, 3 H), 2.19–1.92 (m, 6 H), 1.69–1.43 (m, 4 H); mass spectrum, m/e 304 (M^+), 220 (M – 84), 173 (M – 131). Anal. Calcd for $C_{17}H_{20}OS_2$: C, 67.07; H, 6.62. Found: C, 66.77; H, 6.54.

1,2,3,4-Tetrahydrophenanthren-4-one Trimethylene Dithioketal (29): colorless crystal; mp 166.0–167.0 °C; R_f 0.44 (hexane/EtOAc = 10/1); IR ($CHCl_3$) 2975, 2910, 2840, 1495, 1440, 1410, 1405, 1260 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.99–9.75 (m, 1 H), 7.80–7.05 (m, 5 H), 3.58–1.18 (m, 12 H); mass spectrum, m/e 286 (M^+).

Similar reaction of **19** and **21** resulted in a rapid decomposition to give only intractable polymeric substances.

General Procedure for the Intramolecular Diels–Alder Reactions of Isobenzofurans Generated from Phthalans 16 and 18. The reaction of **16** is described as an illustrative case. To 100 mg (0.27 mmol) of **16** dissolved in 15 mL of toluene at 110 °C was added a solution of CSA (7 mg, 0.03 mmol) in 1 mL of toluene. After the mixture was refluxed for 3 min, solid K_2CO_3 (ca. 50 mg) was added, and the mixture was cooled to room temperature. Ether (70 mL) was added, and the mixture was washed with saturated aqueous $NaHCO_3$ (15 mL) and brine (20 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (silica gel, hexane/EtOAc = 5/1) to give 82 mg (94%) of **25** as a colorless crystal.

Reaction of **18** (158 mg, 0.417 mmol) using 9 mg (0.04 mmol) of CSA followed by the similar workup and silica gel chromatography afforded **29** (17 mg, 14%), **30** (22 mg, 17%) and **28** (85 mg, 65%) in order of elution.

***cis*-1,2,3,4,4a,9,10,10a-Octahydro-4a,9-epoxyphenanthren-4-one Trimethylene Dithioketal (30)**: colorless crystal; mp 166.0–167.5 °C; R_f 0.40 (hexane/EtOAc = 10/1); IR ($CHCl_3$) 2975, 2930, 2840, 1435, 1335, 1255, 1015 cm^{-1}; ^1H NMR ($CDCl_3$), 270 MHz) δ 8.05 (d, J = 6.5 Hz, 1 H), 7.31–6.90 (m, 3 H), 5.04 (d, J = 5.5 Hz, 1 H), 3.27–2.77 (m, 5 H), 2.26–1.55 (m, 10 H); mass spectrum, m/e 304 (M^+), 284 (M – 20), 220 (M – 84), 197 (M – 107), 173 (M – 131). Anal. Calcd for $C_{17}H_{20}OS_2$: C, 67.07; H, 6.62. Found: C, 67.12; H, 6.59.

Similar reactions of **20** and **22** resulted in rapid decomposition to give only intractable polymeric substances.

General Procedure for the Competitive Inter- vs. Intramolecular Diels–Alder Reactions of Alcohols (15, 17, 19, and 21) with Dimethyl Acetylenedicarboxylate (DMAD). The reaction of **15** is described as an illustrative case. To a stirred of 345 mg (1.12 mmol) of **15** and 0.14 mL (1.12 mmol) of DMAD dissolved in 18 mL of toluene at 110 °C was added a solution of CSA (27 mg, 0.11 mmol) in 1 mL of toluene. After the mixture was refluxed with azeotropic separation of water by using a Dean–Stark apparatus, solid K_2CO_3 (50 mg) was added, and the mixture was cooled to room temperature. Ether (100 mL) was added, and the mixture was washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was subjected to column chromatography (silica gel) using hexane/EtOAc (10/1) to give 224 mg (71%) of **25** and 40 mg (8%) of **31** in order of elution.

1-[2-(3-Butenyl)-1,3-dithian-2-yl]-1,4-dihydro-2,3-bis(methoxycarbonyl)-1,4-epoxynaphthalene (31): colorless oil; R_f 0.12 (hexane/EtOAc = 5/1); IR (neat) 3070, 1715, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.99–6.97 (m, 4 H), 6.15–5.51 (m, 1 H), 5.95 (s, 1 H), 5.17–4.80 (m, 2 H), 3.80 (s, 3 H), 3.70 (s, 3 H), 3.45–1.67 (m, 10 H); mass spectrum, m/e 432 (M^+).

The results in the reaction of **17**, **19**, and **21** were summarized in Table II, and the spectroscopic data for the adducts **32–34** are as follows.

1,4-Dihydro-2,3-bis(methoxycarbonyl)-1-[2-(4-pentenyl)-1,3-dithian-2-yl]-1,4-epoxynaphthalene (32): colorless oil; R_f 0.03 (hexane/EtOAc = 10/1); IR ($CHCl_3$) 3070, 1715, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.97–7.68 (m, 1 H), 7.44–6.97 (m, 3 H),

5.94 (s, 1 H), 6.18–5.50 (m, 1 H), 5.18–4.83 (m, 2 H), 3.79 (s, 3 H), 3.71 (s, 3 H), 3.09–1.23 (m, 12 H); mass spectrum, m/e 446 (M^+).

1,4-Dihydro-2,3-bis(methoxycarbonyl)-1-(4-pentenyl)-1,4-epoxynaphthalene (33): colorless oil; R_f 0.20 (hexane/EtOAc = 5/1); IR (neat) 3050, 1710, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.51–6.97 (m, 4 H), 5.91 (s, 1 H), 6.18–5.52 (m, 1 H), 5.22–4.84 (m, 2 H), 3.80 (s, 3 H), 3.75 (s, 3 H), 2.56–1.45 (m, 6 H); mass spectrum, m/e 328 (M^+).

1,4-Dihydro-2,3-bis(methoxycarbonyl)-1-(5-hexenyl)-1,4-epoxynaphthalene (34): colorless oil; R_f 0.27 (hexane/EtOAc = 5/1); IR (neat) 3075, 1720, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45–6.96 (m, 4 H), 5.91 (s, 1 H), 6.06–5.50 (m, 1 H), 5.18–4.76 (m, 2 H), 3.79 (s, 3 H), 3.75 (s, 3 H), 2.57–1.24 (m, 8 H); mass spectrum, m/e 342 (M^+).

General Procedure for the Competitive Inter- vs. Intramolecular Diels–Alder Reactions of Phthalans 16, 18, 20, and 22 with DMAD. The reaction of **16** is described as an illustrative case. To a mixture of 100 mg (0.274 mmol) of **16** and 34 mL (0.274 mmol) of DMAD in 3 mL of toluene at 110 °C was added a solution of CSA (7 mg, 0.027 mmol) in 1 mL of toluene. After 3 min, solid K_2CO_3 (ca. 50 mg) was added, and the mixture was cooled to room temperature. The reaction mixture was diluted with ether (60 mL), washed with saturated aqueous $NaHCO_3$ (15 mL) and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was chromatographed on silica gel (hexane/EtOAc = 10/1) to give 62 mg (77%) **25** and 1 mg (9%) of **31** in the order of elution.

The results of the similar reactions of **18**, **20**, and **22** are summarized in Table II.

Acknowledgment. We thank Hideyuki Akieda for the fundamentally experimental assistance.

Supplementary Material Available: Experimental details for the preparation of **7–10** and their spectroscopic data (8 pages). Ordering information is given on any current masthead page.

Regioselective and Stereoselective Nucleophilic Addition to Electrophilic Vinylcyclopropanes

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Palladium(0) complexes catalyze ring opening of 1,1-diactivated 2-vinylcyclopropanes **2** with concomitant addition of a carbon nucleophile. The reaction is extremely regioselective and stereoselective in that the alkylation occurs syn to the cyclopropane bond being cleaved in [n.1.0] bicyclic systems (n = 3, 4).

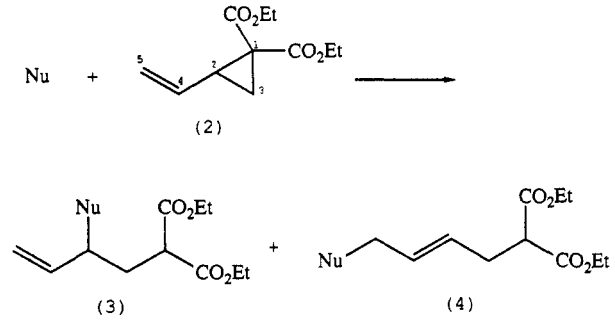
A common tactic in organic synthesis is to cyclopropanate a double bond so that when the strained ring is opened some molecular fragment, or useful functional group, can be introduced. An attractive advantage of this strategy is that one bond of the cyclopropane often may be cleaved selectively due to stereoelectronic control.[1] As a consequence of this, there is considerable interest in new methods for opening cyclopropanes,[2] and subsequently the procedures developed may be applied in total syntheses.[3]

Nucleophilic ring opening of electrophilic vinylcyclopropanes **2** is more difficult to control.[4a] Addition could occur at C^2 or C^5 (using the numbering system shown in Scheme I), and this seems to be governed by the nature of the nucleophile. For instance,[5] thiolate anions (RS^-) preferentially add to C^2 while mercaptyl radicals (RS·) add to C^5.[6] In some cases the selectivity is poor, thus diminishing the utility of this type of reaction; dimethylsodiomalonate, for example, reacts with cyclopropane **2** to give a mixture of the tetraesters **3** and **4** (Scheme I).[4]

This research was undertaken in order to develop mild, selective methods of adding stabilized carbanionic nucleophiles to activated vinylcyclopropanes. Stoichiometric quantities of certain transition-metal complexes react readily with cyclopropanes and vinylcyclopropanes.[7] Catalytic amounts of palladium complexes can cause (i) isomerization of dienylcyclopropanes[8] and dienylaziridines[9] to five-membered ring systems and (ii) addition of amines to vinylcyclopropanes;[10] therefore, palladium catalysis was an obvious starting point for this study.

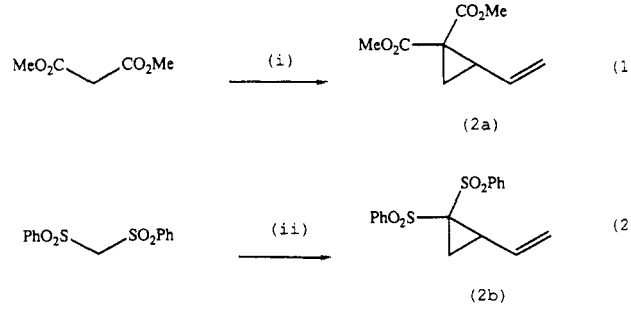
The diesters **2a** and **2b** were conveniently prepared by literature methods[11] or via zerovalent palladium catalysis as described in eq 1, Scheme II. In palladium-catalyzed allylic substitution reactions of the latter type[12] alkoxide ions are formed from the carbonate leaving groups; hence, it is not necessary to add base or to isolate the monosub-

Scheme I[a]



[a] When Nu = $NaCH(CO_2Et)_2$, the ratio of **3** to **4** is 5:1.[4]

Scheme II[a]



[a] Key: (i) MeO_2CO⌒=⌒OCO_2Me, 2 mol % $Pd(PPh_3)_4$, THF, 20 °C, 12 h; (ii) Br⌒=⌒Br, 2.05 $N(n\text{-}Bu)_4OH$(aq), CH_2Cl_2, 20 °C, 4 days.

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