= 5.5 Hz, 8.0 Hz, 1 H, –CONCH–), 5.05 (s, 2 H, OCH_2Ph), 7.36 (s, 5 H, aromatic), 7.7 (d, J = 8.0, 1 H, –CONH). Anal. Calcd for $C_{12}H_{13}N_2O_7SNa·H_2O$: C, 38.92; H, 4.08; N, 7.56; H_2O, 4.86. Found: C, 38.98; H, 4.14; N, 7.69; H_2O, 5.14.

Sodium (3*S*,4*S*)-3-(Benzyloxycarboxamido)-4-[(carbamoyloxy)methyl]-2-oxoazetidine-1-sulfonate (27). A solution of azetidinone **25** (2.42 g, 4.2 mmol) in dry methylene chloride (40 mL) was cooled to 0 °C, and chloroacetylisocyanate (0.42 mL, 8.4 mmol) was added slowly under argon. The reaction mixture was stirred at 0 °C for 1 h, and sodium *N*-methyldithiocarbamate (1.2 g, 8.16 mmol) in water (15 mL) was added. The mixture was stirred vigorously at room temperature for 1 h. The organic layer was separated, and the aqueous phase was extracted once with methylene chloride. The combined organic extracts were dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The residue was dissolved in 40 mL of ethanol/water (1:2) and stirred with about 30 mL of AG 50W-X4 resin (100–200 mesh, Na^+ form) for 15 min. The resin was removed by filtration and washed with water (30 mL). The filtrate was concentrated under high vacuum to about half of the original volume and washed with ethyl acetate (2 × 10 mL). The aqueous solution was evaporated to dryness under high vacuume. The solid residue was slurried with methanol and filtered. The crystals were washed with cold methanol and ether and dried to give 580 mg (36%) of azetidinone **27**. The mother liquor was concentrated and applied to a column of Diaion (60 mL), which was eluted with water, followed by 5% ethanol/water. The desired fractions were combined, concentrated, and slurried with acetone to give an additional 220 mg (14%) of product: mp 206–207 °C dec; $[\alpha]^{25}_D$ +31.23° (*c* 0.5796, H_2O); IR (KBr) ν_{max} 1797, 1715, 1694, 1273, 1254 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.90–4.35 (m, 3 H, –$CHCH_2O$–), 4.91 (dd, J = 5.5 Hz, 8.0 Hz, 1 H, –CONCH–), 5.06 (s, 2 H, OCH_2Ph), 6.4 (br s, 2 H, $CONH_2$), 7.38 (s, 5 H, aromatic) 7.98 (d, J = 8.0 Hz, 1 H, –CONH–). Anal. Calcd for $C_{13}H_{14}N_3O_8SNa$: C, 39.50; H, 3.57; N, 10.63; S, 8.11. Found: C, 39.53; H, 3.77; N, 10.55; S, 8.30.

(3*S*,4*S*)-3-Amino-4-[(carbamoyloxy)methyl]-2-oxoazetidine-1-sulfonic Acid (2). The mixture of azetidinone **27** (1.97 g, 5 mmol) and 0.4 g of 10% Pd/C in 70 mL of methanol/H_2O (1:1) was treated with hydrogen at atmospheric pressure for 1 h. The catalyst was removed by filtration, and the filtrate was concentrated to about 10 mL. The solution, chilled in an ice bath, was adjusted to pH 2 with 1 N HCl, and ethanol (10 mL) was added. Crystals were collected to give 1.14 g (95% yield) of **2**: mp 208–209 °C dec; $[\alpha]^{25}_D$ –6.09° (*c* 0.5, Me_2SO); IR (KBr) ν_{max} 3470, 3355, 3100–2635, 1785, 1742, 1708, 1532, 1248, 1208, 1050 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 4.08–4.24 (m, 1 H, >CH), 4.24–4.44 (m, 2 H, –CH_2O–), 4.68 (d, J = 6.3 Hz, 1 H, >(N)CH), 6.52 (s, 2 H, $CONH_2$), 8.5 (br s, 3 H, –$^+NH_3$). Anal. Calcd for $C_5H_9N_3O_6S$: C, 25.11; H, 3.79; N, 17.57; S, 13.40. Found: C, 25.27; H, 3.84; N, 17.44; S, 13.66.

Acknowledgment. We thank Mr. P. Weinert of our Technical Development Department for the supply of calcium L-threonate and 5,6-*O*-isopropylidene-L-ascorbic acid. We are also indebted to the personnel of our Physical Chemistry Department for providing the spectroscopic and microanalytical data.

Regioselective Synthesis of Dihydrofurans from 2,2-Dibromo 1,3-Diones and Olefins Using Copper

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2,2-Dibromo 1,3-diones reacted with copper powder and olefin to give 2,3-dihydrofuran derivatives in a highly regioselective fashion. Acetylenes and 1,3-dienes also reacted with 2,2-dibromo 1,3-diones and copper to afford furan derivatives and 2-vinyl-2,3-dihydrofuran derivatives, respectively. In benzene copper was converted into copper(I) bromide during the course of reaction, whereas in Me_2SO copper was converted into copper(II) bromide. The reactions with (*E*)- and (*Z*)-β-methylstyrene proceeded in a nonstereospecific way and only the *E* isomer of the dihydrofuran derivative was obtained. Hammett study with substituted styrenes gave a ρ value of –0.90. A mechanism involving a radical intermediate rationalizes the results.

1,3-Dipolar addition reactions are an important tool to construct various heterocyclic compounds as well as to functionalize carbon–carbon unsaturated bonds.[1,2] It is well-known that α-keto carbenes and α-keto carbenoids serve as 1,3-dipoles,[3] and several methods for their preparation have been developed. For example, thermolysis of diazo ketones in the presence of trapping agents such as olefins, acetylenes, and nitrile is reported to produce the corresponding cycloadducts.[4] Copper catalysts promote decomposition of diazo ketones.[5] It is also reported that α-elimination of dibromo ketones affords α-keto carbenes[6] which are effectively trapped by olefins.[6a] Al-

(1) For example: Desimoni, G.; Tacconi, G.; Barco, A.; Pollini, G. P. "Natural Products Synthesis Through Pericyclic Reactions"; American Chemical Society: Washington, DC, 1983; Chapter 4.
(2) (a) Firestone, R. A. *Tetrahedron* **1977**, *33*, 3009. (b) Huisgen, R. *J. Org. Chem.* **1976**, *41*, 403.
(3) Reference 5d and references cited therein.
(4) (a) Huisgen, R.; Binsch, G.; Ghosez, L. *Chem. Ber.* **1964**, *97*, 2628. (b) Huisgen, R.; Sturm, H. J.; Binsch, G. *Ibid.* **1964**, *97*, 2864. (c) Huisgen, R.; Binsch, G.; Koenig, H. *Ibid.* **1964**, *97*, 2868. (d) Huisgen, R.; Binsch, G.; Koenig, H. *Ibid.* **1964**, *97*, 2884. (e) Binsch, G.; Huisgen, R.; Koenig, H. *Ibid.* **1964**, *97*, 2893. (f) Dworschak, H.; Weygand, F. *Ibid.* **1968**, *101*, 302.
(5) (a) Wenkert, E.; Alonso, M. E.; Buckwalter, B. L.; Chou, K. J. *J. Am. Chem. Soc.* **1977**, *99*, 4778. (b) Wenkert, E.; Alonso, M. E.; Buckwalter, B. L.; Sanchez, E. L. *Ibid.* **1983**, *105*, 2021. (c) Alonso, M. E.; Jano, P.; Hernandez, M. I.; Greenberg, R. S.; Wenkert, E. *J. Org. Chem.* **1983**, *48*, 3047. (d) Alonso, M. E.; Morales, A.; Chitty, A. W. *Ibid.* **1982**, *47*, 3747.
(6) (a) Scott, L. T.; Cotton, W. D. *J. Am. Chem. Soc.* **1973**, *95*, 5416. (b) Scott, L. T.; Cotton, W. D. *Ibid.* **1973**, *95*, 2708. See also ref. 9.

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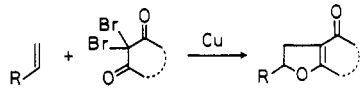
Table I. Reaction of 2,2-Dibromo 1,3-Diones with Styrene[a]

dibromo dione	solvent	temp, °C	product	yield, %[b]
	PhH	70		(96)
	Me_2SO	rt[d]		(99)
	PhH	80		80
	Me_2SO	rt[d]		56
	PhH	80		59
	PhH	80		26
	Me_2SO	30		trace
	PhH	80		c
	Me_2SO	30		c
	PhH	70		c

[a] Dibromo dione (1.5 mmol), styrene (1.0 mmol), and copper (3.0 mmol) were allowed to react in benzene. In Me_2SO dibromo dione (1.5 mmol), styrene (1.0 mmol), and copper (1.5 mmol) were allowed to react. [b] Isolated yield based on styrene. Yields in parentheses were determined by VPC analysis. [c] Dihydrofuran derivative was not detected. [d] rt = room temperature.

though mechanistic aspects of keto carbenes and keto carbenoids have been explored extensively, their application to organic synthesis has been rather limited. In searching for a mild method to generate keto carbenoids, we have found that reduction of 2,2-dibromo 1,3-diones with copper powder in the presence of olefin afforded 2,3-dihydrofurans (formal 1,3-dipolar adducts) eq 1.[7] Herein we report full details of the reaction.



(1)

Results and Discussion

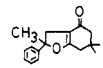
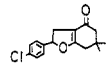
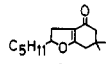
Reaction of 2,2-Dibromo Diones with Olefins. 2,2-Dibromo-5,5-dimethyl-1,3-cyclohexanedione (dibromodimedone), which was readily prepared by bromination of 5,5-dimethyl-1,3-cyclohexanedione (dimedone), was chosen as a model to explore the reaction. Styrene was chosen as an acceptor. After activation of copper powder (3.0 mmol) by the reaction with a small amount of iodine in benzene, dibromodimedone (1.5 mmol) and styrene (1.0 mmol) were added. The mixture was allowed to react at 70 °C. During the course of the reaction, copper powder was gradually consumed. After 2 h 2-phenyl-4-oxo-6,6-dimethyl-2,3,4,5,6,7-hexahydrobenzofuran (1), a formal 1,3-dipolar adduct, was obtained in good yield (GLC analysis).

The reaction was also performed by using a dimethyl sulfoxide (Me_2SO) as the solvent. Copper powder (1.5 mmol), dibromodimedone (1.5 mmol), and styrene (1.0 mmol) were allowed to react at 20–30 °C for 4 h to obtain the dihydrofuran derivative in 99% yield (GLC analysis). Activation of copper powder by iodine was not necessary in this case. The choice of the solvent depends on the nature of substrates.

The reaction can be applied to other 2,2-dibromo 1,3-diones (Table I). Cyclic dibromo diones reacted smoothly with styrene to give the corresponding dihydrofuran derivatives. However, reactivity of acyclic dibromo diones was low. For example, the reaction of 3,3-dibromo-2,4-pentanedione with styrene gave the corresponding dihydrofuran derivative (4) only in 26% yield. 2,2-Dibromo-1,3-diphenyl-1,3-propanedione did not afford the cycloadduct, although both dibromide and copper were consumed. The reason is not clear at present.

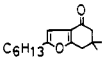
Various olefins reacted with 2,2-dibromo 1,3-diones and copper in a similar fashion to give the corresponding dihydrofuran derivatives (Table II). Although alkyl-sub-

Table II. Reaction of Dibromodimedone with Olefins[a]

olefin	solvent	temp, °C	product	yield, %[b]
$C_6H_5CH=CH_2$	PhH	70		96 (88)
	Me_2SO	rt[d]		99
$C_6H_5C(CH_3)=CH_2$	PhH	70		99
p-$CH_3C_6H_4CH=CH_2$	PhH	70		70
p-$ClC_6H_4CH=CH_2$	PhH	70		85
m-$CF_3C_6H_4CH=CH_2$	PhH	70		61
(Z)-$PhCH=CHCH_3$	PhH	70		47
(E)-$PhCH=CHCH_3$	PhH	70		50
	PhH	70		37
$C_5H_{11}CH=CH_2$	PhH	80		30
$CH_3COCH=CH_2$	Me_2SO	30		32
	Me_2SO	rt[d]		26[c]

[a] See footnote a of Table I. [b] Yields were determined by VPC analysis. Yield in parentheses was isolated yield. [c] Cu_2Br_2 (1.5 mmol) was used instead of copper. [d] rt = room temperature.

Table III. Reaction of Dibromodimedone with 1,3-Dienes and Acetylenes[a]

diene or acetylene	solvent	temp, °C	product	yield, %[b]
	Me_2SO	rt[d]		73
	Me_2SO	30		81
	Me_2SO	30		40
	PhH	70		48[c]
$C_6H_5C\equiv CH$	PhEt	reflux		65
$C_6H_5C\equiv CCH_3$	PhEt	reflux		18
$C_6H_{13}C\equiv CH$	PhEt	reflux		34

[a] See footnote a of Table I. [b] Yields were determined by VPC. [c] E/Z = 60/40. [d] rt = room temperature.

(7) Yoshida, J.; Yano, S.; Ozawa, T.; Kawabata, N. *Tetrahedron Lett.* **1984**, *25*, 2817.

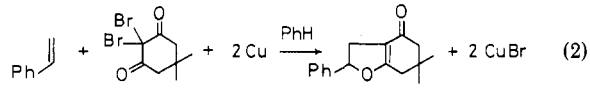
stituted olefin, enone, and enol ether were effective as acceptors, styrene derivatives were the most effective olefins among the examined.

The reaction exhibits high regioselectivity. The oxygen atom of the dibromo dione added exclusively onto the more substituted carbon of terminal olefins. For example, styrene and 1-heptene afforded 2-phenyl- and 2-pentyl-2,3-dihydrofuran derivatives, respectively. β-Methylstyrene afforded the 2-phenyl-3-methyl-2,3-dihydrofuran derivatives (**9**) regioselectively. The other regioisomer was not detected at all.

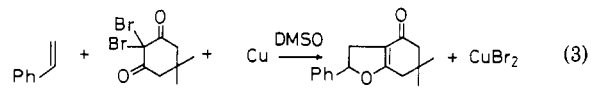
Reaction of 2,2-Dibromo Diones with 1,3-Dienes and Acetylenes. 1,3-Dienes reacted with the 2,2-dibromo 1,3-dione in a 1,2-fashion to afford vinyldihydrofuran derivatives. As shown in Table III, the regioselectivity is outstanding. In virtually all cases examined only one regioisomer was obtianed.

Acetylenes also served as acceptors and the corresponding furan derivatives were obtained. Regioselectrivity was high, and terminal acetylenes afforded 2-substituted furans exclusively. The reactions required higher temperatures than those with olefins, and, therefore, ethylbenzene was used as the solvent instead of benzene. This indicates the lower reactivity of acetylenes as opposed to olefins. A similar trend is observed in general for cycloaddition reactions.[2a]

Stoichiometry of the Reaction. For elucidation of the reaction mechanism, it is important to know the stoichiometry of the reaction. Thus, we examined the fate of copper metal after the reaction. Dibromodimedone and styrene were allowed to react with copper powder in benzene under the normal conditions. After the reaction, the mixture was filtered, and the solid material was separated by filtration. The pale yellowish green powder obtained was identified as copper(I) bromide by its X-ray powder analysis. In the reaction in Me_2SO, however, copper metal was converted into copper(II) bromide which was identified by comparison of its IR spectrum with that of an authentic sample.[8] The results indicate that copper metal acted as a reductive debrominating agent[9] in both cases. Thus the present reaction is considered to obey the following stoichiometries depending on the solvent eq 2 and 3.



(2)



(3)

Stereochemistry. Reactions of (*E*)- and (*Z*)-β-methylstyrenes with dibromodimedone and copper were carried out to examine the stereochemistry of the present reaction. From both olefins were obtained (*E*)-2-phenyl-3-methyl-4-oxo-6,6-dimethyl-2,3,4,5,6,7-hexahydrobenzofuran (**9**) exclusively (eq 4), indicating that the reaction proceeded in a nonstereospecific way. The stereochemistry of the product was clearly assigned as *E* based upon ^1H NMR data. The methyl group at δ 1.35 compared more favorably with δ 1.12 of the C-4 methyl of (*E*)-2-phenyl-3,4,5-trimethyl-2,3-dihydrofuran than with δ 0.50 of the corresponding *Z* isomer, in which the cis methyl group is shielded by the phenyl group (see Experimental Section for full details). Isomerization of both olefins and starting materials was not detected under the conditions. Unfortunately the possibility of isomerization of the product cannot be precluded, because we did not have the corresponding *Z* isomer of the dihydrofuran derivative at hand, and, therefore, we could not carry out its isomerization experiment. However, such isomerization seems unlikely, because the reaction conditions are quite mild. Therefore it is reasonably considered that equilibration took place during the course of the reaction which involves a freely rotating intermediate.

(4)

Reaction of Dibromo Keto Ester. The reaction of a dibromo keto ester was also carried out in order to examine the scope of the present reaction. When ethyl dibromoacetoacetate was allowed to react with styrene and copper in Me_2SO, both dihydrofuran (**22**) and cyclopropane derivatives (**21a** and **21b**) were obtained (eq 5). No isomerization of the cyclopropane derivatives to the dihydrofuran derivative was observed under the reaction conditions, indicative of direct formation of both cyclopropane and dihydrofuran derivatives. Reaction of dibromomalonate with olefins is known to give cyclopropane derivatives.[10] Inspection of these facts implies that only the keto carbonyl group, not the ester carbonyl group, can participate in cyclization to form a dihydrofuran ring under the conditions[11] and also that the second keto carbonyl group plays some role in dihydrofuran formation.

(5)

Reaction Mechanism. The following points seem to be helpful for the elucidation of the reaction mechanism. (1) Direct formation of the dihydrofuran is suggested by the reaction of the dibromo keto ester. Isomerization of initially formed cyclopropane to dihydrofuran[12,13] is less

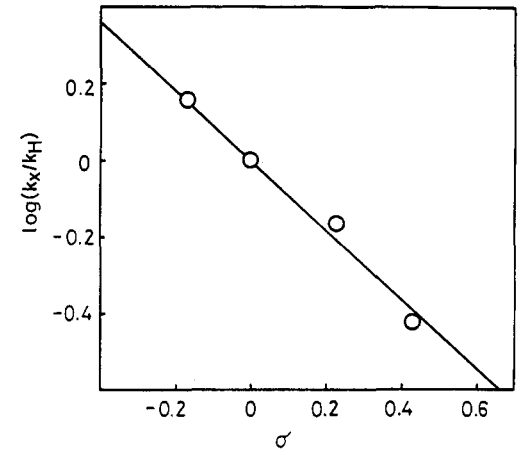


Figure 1. Hammett plot for the reaction of dibromodimedone with substituted styrenes and copper.

(8) Meek, D. W.; Sttaub, D. K.; Drago, R. S. *J. Am. Chem. Soc.* **1960**, *82*, 6013.

(9) Kawabata, N.; Kamemura, I.; Naka, M. *J. Am. Chem. Soc.* **1979**, *101*, 2139 and references cited therein.

(10) (a) Kawabata, N.; Tanimoto, M. *Tetrahedron* **1980**, *36*, 3517. (b) Kawabata, N.; Yano, S.; Hashimoto, J.; Yoshida, *J. Bull. Chem. Soc. Jpn.* **1981**, *54*, 2539.

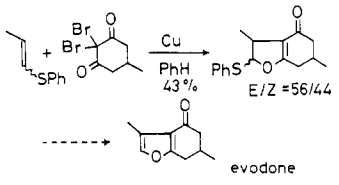
(11) See ref 13a.

(12) Keto carbenoid generated by α-elimination of ω,ω-dibromoacetophenone with copper was trapped by olefin to form cyclopropane derivative. Kawabata, N.; Fujii, T.; Naka, M.; Yamashita, S. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1005.

likely. (2) The stereochemical study suggests a mechanism involving a freely rotating intermediate. A concerted mechanism seems to be ruled out. (3) Both olefins with electron-withdrawing substituents such as methyl vinyl ketone and olefins with electron-donating substituents such as 1-heptene afforded 2-substituted 2,3-dihydrofuran derivatives. Therefore, carbanion and carbocation intermediates are unlikely. The Hammett ρ value of −0.90 (Figure 1) suggests that the reaction proceeds via a radical process rather than an ionic process. The higher reactivity of conjugated olefins such as styrene derivatives and 1,3-dienes rather than nonconjugated olefins is also consistent with a radical mechanism. (4) The regioselectivity exerted by various olefins and 1,3-dienes can be explained if we consider the most stable formal diradical intermediate.[2a] Frontier electron densities for radical reactions also rationalize the observed regioselectivity.[14] Radical attack on olefins or 1,3-dienes seems to be a regiochemistry-controlling step. On the basis of these arguments, a possible mechanism for the present reaction involves the following steps. (1) Reductive debromination of dibromo dione by copper produces a diketo carbene intermediate which may or may not interact with copper ion in the reaction medium. (2) This diketo carbene acts as a diradical[2a] and adds to the olefin or diene to give the freely rotating diradical intermediate. (3) The diradical intermediate then cyclizes at carbonyl oxygen to form dihydrofuran derivatives.

Synthetic Application. Several methods have been reported for synthesis of dihydrofuran[15] and furan[16] derivatives. In comparison of these conventional methods, several characteristic advantages of the present reaction should be mentioned: (1) The reaction conditions are mild. (2) The procedure is simple, and all the reagents employed can be handled without special care which is required for diazo ketones. (3) The regioselectivity is extremely high. Only one regioisomer is usually obtained.

To illustrate one of the unique synthetic applications of this method, we have developed a new simple route to evodone[17] (eq 6). 2,2-Dibromo-5-methyl-1,3-cyclohexanedione was allowed to react with 1-(phenylthio)-1-propene and copper in benzene to obtain 2-(phenylthio)-3-methyl-4-oxo-6-methyl-2,3,4,5,6,7-hexahydrobenzofuran (**23**) in 43% yield. The reaction was regioselective, but a mixture of stereoisomers was formed in a ratio of E/Z = 56/44. Since it is reported that both stereoisomers can be converted into evodone by oxidation followed by elimination,[17] formal synthesis of evodone is accomplished.



(6)

(13) Thermal, photochemical, and aluminum oxide assisted rearrangement of cyclopropyl ketone to dihydrofuran is reported: (a) McGreer, D. E.; McKinley, J. W. *Can. J. Chem.* **1973**, *51*, 1487. (b) Alonso, M. E.; Morales, A. *J. Org. Chem.* **1980**, *45*, 4530.

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(15) (a) Albin, P.; Blum, J.; Dunkelblum, E.; Sasson, Y. *J. Org. Chem.* **1975**, *40*, 2402. (b) Heiba, E. I.; Dessau, R. M. *Ibid.* **1974**, *39*, 3456. (c) Uemura, S.; Ichikawa, K. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 1016. (d) Ichikawa, K.; Uemura, S. *J. Org. Chem.* **1967**, *32*, 493.

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(17) Miyashita, M.; Kumazawa, T.; Yoshikoshi, A. *J. Org. Chem.* **1980**, *45*, 2945.

Experimental Section

General Methods. Proton NMR spectra were determined in carbon tetrachloride (CCl_4) or deuterio:chloroform ($CDCl_3$) on a Varian T-60A (60 MHz) instrument or a Varian XL-200 (200 MHz) spectrometer. Chemical shifts are reported in δ units, parts per million (ppm), from tetramethylsilane (Me_4Si). Infrared (IR) spectra were determined on a Hitachi 215 grating spectrometer and are reported in cm^{-1}. Mass spectra were obtained on a JEOL JMS-D300 mass spectrometer connected with a JEOL JGC-20K gas chromatograph equipped with a 1-m glass column packed with OV-17 (1%) on Chromosorb B and a JMA-200 data processing system, or a Hitachi M-80A mass spectrometer connected with a Hitachi M-003 data processing system. Ionization potential was 70 eV. Gas chromatography was performed on a Shimadzu GC-4B or GC-4C gas chromatograph. Column A refers to a 1 m × 3 mm column packed with Silicone DC 550 (5%) on Celite 545. Column B refers to a 1 m × 3 mm column packed with PEG 20M (2.5%) on Celite 545. The flow rate was normally 20 mL/min. Plastic-support precoated plates (Merk Silica gel 60 F_{254}, 0.2 mm) were used for analytical thin-layer chromatography (TLC). Merk Silica gel 60 F_{254} containing $CaSO_4$ was employed for preparative TLC. Flash chromatography was performed on Wako gel C-200 or C-300 according to the method reported by Still.[18] Melting points are uncorrected.

Copper powder (Nakarai Chemicals) was used as obtained commercially. *p*-Methylstyrene,[19] *p*-chlorostyrene,[19] *m*-(trifluoromethyl)styrene,[19] (*E*)-β-methylstyrene,[19] and (*Z*)-β-methylstyrene[19] were prepared according to the literature methods with minor modifications. (Phenylmethyl)acetylene was prepared by metalation of phenylacetylene with ethylmagnesium bromide followed by treatment with methyl iodide. Styrene, 1-octyne, and phenylacetylene were purified by distillation before use. 2,2-Dibromo-5,5-dimethyl-1,3-cyclohexanedione,[20] ethyl dibromoacetoacetate,[21] 2,2-dibromo-5-methyl-1,3-cyclohexanedione,[22] 2,2-dibromo-1,3-cyclohexanedione,[23] and 2,2-dibromo-1,3-diphenyl-1,3-propanedione,[24] were prepared according to the literature. Dimethyl sulfoxide (Me_2SO) was dried over calcium hydride and distilled before use. Other chemicals were used as obtained commercially.

Preparation of 3,3-Dibromo-2,4-pentanedione. To a solution of acetylacetone (990 mg, 9.89 mmol) in 20 mL of carbon tetrachloride was added *N*-bromosuccinimide (NBS) (4.391 g, 24.7 mmol), and the mixture was stirred at 60 °C for 7.5 h. Filtration followed by removal of the solvent and bulb-to-bulb distillation (80 °C, 1 mmHg) yielded 2.140 g (84%) of the title compound as a pale yellow oil: ^1H NMR (60 MHz, CCl_4) δ 2.57 (s, 6 H); IR (neat) 3010 (w), 2930 (w), 1745 (s), 1727 (s), 1430 (m), 1362 (s), 1198 (s), 1175 (s), 1010 (w), 790 (m), 750 (s) cm^{-1} (lit.[25] IR 1737, 1714, 1407, 1360 cm^{-1}).

Preparation of 2,2-Dibromo-1-phenyl-1,3-butanedione. To a solution of 1-phenyl-1,3-butanedione (1.627 g, 10.0 mmol) in 20 mL of carbon tetrachloride was added NBS (4.561 g, 25.6 mmol), and the mixture was stirred at 70 °C for 38.5 h. Filtration followed by removal of the solvent and flash chromatography (9:1 hexane/ethyl acetate) yielded 2.525 g (79%) of the title compound as a pale yellow oil: ^1H NMR (60 MHz CCl_4) δ 2.47 (s, 3 H), 7.3–7.6 (m, 3 H), 7.9–8.2 (m, 2 H); IR (neat) 3060 (m), 2925 (w), 1740 (s), 1690 (s), 1663 (s), 1598 (s), 1580 (s), 1448 (s), 1360 (s), 1225 (s), 1190 (s), 1160 (s), 1045 (m), 1000 (m), 970 (m), 933 (w), 815 (s), 760 (m), 682 (s) cm^{-1}.

General Procedure for the Reaction of 2,2-Dibromo 1,3-Diones with Olefins or Acetylenes and Copper. Method A. A 20-mL one-necked flask equipped with a magnetic stirring bar and a reflux condenser was charged with copper powder (3.0

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mmol), iodine (0.05 mmol), and benzene (1.0 mL). The mixture was stirred at room temperature until the color of the iodine disappeared (usually 10 min). The 2,2-dibromo 1,3-dione (1.5 mmol) and an olefin or an acetylene (1.0 mmol) were added, and the resulting mixture was heated to the stated temperature. After the reaction was completed, the reaction mixture was cooled to room temperature and filtered. The solid material was washed with benzene (3 × 5 mL), and the filtrate and washings were combined. After removal of the solvent, the residue was purified by flash chromatography or preparative TLC. The solvent reported for R_f of the corresponding product was used for elution. In some cases the products were purified by preparative GLC. Reactions using ethylbenzene as solvent were performed in a similar fashion.

Method B. A 20-mL one-necked flask equipped with a magnetic stirrer was charged with copper powder (1.5 mmol), 2,2-dibromo 1,3-dione, an olefin or an acetylene (1.0 mmol), and dimethyl sulfoxide (Me_2SO), and the resulting mixture was stirred at the stated temperature for a given period. After the reaction was completed, the reaction mixture was partitioned between ether (10 mL) and water (10 mL). The aqueous phase was extracted with ether (3 × 5 mL), and the combined extracts were dried over Na_2SO_4. The solvent was removed, and the crude product obtained was purified by flash chromatography, preparative TLC, or preparative GLC.

Synthesis of 2-Phenyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran (3). Typical Procedure. A 20-mL flask was charged with copper powder (193 mg, 3.03 mmol), iodine (8.5 mg, 0.033 mmol), and benzene (1.0 mL), and the mixture was stirred at room temperature for 10 min. During this period, the color of iodine disappeared. 2,2-Dibromo-1,3-cyclohexanedione (420 mg, 1.55 mmol) and styrene (118 mg, 1.13 mmol) were added, and the resulting mixture was heated at reflux for 2 h. After having been cooled to room temperature, the mixture was filtered and the solid materials were washed with benzene (3 × 5 mL). The filtrate and the washing were combined, and the solvent was removed on a rotary evaporator. The crude product obtained was purified by flash chromatography (1:1 hexane/ethyl acetate) to give 144 mg (59% based on styrene) of the title compound as a colorless oil: TLC R_f 0.22 (1:1 hexane/ethyl acetate); n^{30}_D 1.5833; ^{1}H NMR (60 MHz, CCl_4) δ 1.8–2.85 (m, 6 H), 2.85–3.65 (m, 2 H), 5.75 (d of d, J = 10, 11 Hz, 1 H), 7.35 (br s, 5 H); IR (neat) 3030 (w), 2940 (m), 2870 (w), 1633 (s), 1453 (w), 1402 (m), 1360 (w), 1232 (m), 1181 (m), 1058 (w), 755 (w), 698 (w) cm^{-1}; mass spectrum, calcd for $C_{14}H_{14}O_2$ 214.0994, found 214.1001.

2-Phenyl-4-oxo-6,6-dimethyl-2,3,4,5,6,7-hexahydrobenzofuran (1): TLC R_f 0.52 (1:1 hexane/ethyl acetate); GLC t_R 7.0 min (column A, T = 200 °C); n^{30}_D 1.5561; ^{1}H NMR (60 MHz, CCl_4) δ 1.16 (s, 6 H), 2.26 (br s, 2 H), 2.3–2.4 (m, 2 H), 2.6–3.6 (m, 2 H), 5.75 (d of d, J = 8.4, 10.4 Hz, 1 H), 7.32 (br s, 5 H); IR (neat) 3025 (w), 2950 (m), 2870 (w), 1710 (m), 1630 (s), 1400 (s), 1220 (s), 755 (m), 695 (m) cm^{-1}. Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.20; H, 7.36.

2-Phenyl-4-oxo-6-methyl-2,3,4,5,6,7-hexahydrobenzofuran (2): GLC t_R 11 min (column B, T = 200 °C); TLC R_f 0.33 (1:1 hexane/ethyl acetate); n^{30}_D 1.5685; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.06 (d, J = 5.6 Hz, 3 H), 1.95–2.6 (m, 5 H), 2.78 (d of d, J = 8.2, 14.5 Hz, 1 H), 3.15–3.25 (m, triplet like, 1 H), 5.65–5.75 (m, triplet like, 1 H), 7.28 (br s, 5 H); IR (neat) 3060 (w), 3030 (w), 2955 (m), 2925 (m), 2875 (m), 1632 (s), 1455 (m), 1420 (m), 1403 (s), 1253 (m), 1218 (s), 1053 (m), 778 (m), 699 (m) cm^{-1}; mass spectrum, calcd for $C_{15}H_{16}O_2$ 228.1151, found 228.1170.

2-Phenyl-4-acetyl-5-methyl-2,3-dihydrofuran (4): GLC t_R 4.0 min (column B, T = 180 °C); TLC R_f 0.22 (4:1 hexane/ethyl acetate); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.21 (s, 3 H), 2.31 (t, J = 1.5 Hz, 3 H), 2.90–3.02 (m, 1 H), 3.32–3.45 (m, 1 H), 5.59 (d of d, J = 10.7 and 8.4 Hz, 1 H), 7.14–7.47 (m, 5 H); IR (neat) 2930 (w), 1673 (m), 1610 (s), 1397 (m), 1368 (m), 1230 (m), 699 (m) cm^{-1}; mass spectrum calcd for $C_{13}H_{14}O_2$ 202.0994, found 202.1011.

This compound has also been reported by Ichikawa and Uemura:[15d] ^{1}H NMR (60 MHz) δ 2.20 (s, 3 H), 2.31 (t, J = 1.5 Hz, 3 H), 2.92 (m, 1 H), 3.42 (m, 1 H), 5.59 (d of d, J = 10.4, 8.6 Hz, 1 H), 7.32 (m, 5 H).

2-Methyl-2-phenyl-4-oxo-6,6-dimethyl-2,3,4,5,6,7-hexahydrobenzofuran (5): GLC t_R 6.4 min (column A, T = 200 °C); n^{30}_D 1.5472; ^{1}H NMR (60 MHz, CCl_4) δ 1.10 (s, 3 H), 1.14 (s, 3 H), 1.65 (s, 3 H), 1.9–2.2 (m, 2 H), 2.2–2.5 (m, 2 H), 2.8–3.1 (m, 2 H), 7.25 (br s, 5 H); IR (neat) 3070 (w), 3030 (w), 2960 (s), 2875 (m), 1640 (s), 1400 (s), 1240 (s), 1030 (s), 760 (m), 700 (m) cm^{-1}; mass spectrum, calcd for $C_{17}H_{20}O_2$ 256.1463, found 256.1473.

2-(*p*-Methylphenyl)-4-oxo-6,6-dimethyl-2,3,4,5,6,7-hexahydrobenzofuran (6): GLC t_R 7.5 min (column A, T = 200 °C); n^{30}_D 1.5519; ^{1}H NMR (60 MHz, CCl_4) δ 1.14 (s, 6 H), 2.0–2.2 (m, 2 H), 2.2–2.4 (m, 2 H), 2.34 (s, 3 H), 2.7–3.25 (m, 2 H), 5.67 (t, J = 9.4 Hz, 1 H), 7.09 (br s, 4 H); IR (neat) 3030 (w), 2970 (s), 2885 (m), 1640 (s), 1405 (s), 1230 (s), 1175 (m), 1050 (m), 820 (m) cm^{-1}; mass spectrum, calcd for $C_{17}H_{20}O_2$ 256.1463, found 256.1468.

2-(*p*-Chlorophenyl)-4-oxo-6,6-dimethyl-2,3,4,5,6,7-hexahydrobenzofuran (7): GLC t_R 9.2 min (column A, T = 210 °C); n^{30}_D 1.5632; ^{1}H NMR (60 MHz, CCl_4) δ 1.15 (s, 6 H), 2.15 (br s, 2 H), 2.2–2.4 (m, 2 H), 2.6–3.5 (m, 2 H), 5.66 (d of d, J = 10.8, 7.9 Hz), 7.27 (br s, 4 H); IR (neat) 3050 (w), 2965 (m), 2890 (w), 1640 (s), 1500 (m), 1405 (s), 1225 (s), 1095 (m), 830 (m) cm^{-1}; mass spectrum, calcd for $C_{16}H_{17}ClO_2$ 276.0916, found 276.0912.

2-(*m*-(Trifluoromethyl)phenyl)-4-oxo-6,6-dimethyl-2,3,4,5,6,7-hexahydrobenzofuran (8): GLC t_R 3.8 min (column A, T = 200 °C); n^{30}_D 1.5100; ^{1}H NMR (60 MHz, CCl_4) δ 1.16 (s, 6 H), 2.16 (br s, 2 H), 2.36 (br s, 2 H), 2.7–3.4 (m, 2 H), 5.80 (t with fine couplings, J = 9.0 Hz, 1 H), 7.52 (br s, 4 H); IR (neat) 3070 (vw), 2970 (m), 2880 (w), 1640 (s), 1405 (m), 1335 (m), 1225 (m), 1170 (m), 1130 (m), 805 (m), 700 (m) cm^{-1}; mass spectrum, calcd for $C_{17}H_{17}F_3O_2$ 310.1181, found 310.1182.

2-Phenyl-3-methyl-4-oxo-6,6-dimethyl-2,3,4,5,6,7-hexahydrobenzofuran (9): GLC t_R 5.6 min (column A, T = 200 °C); n^{30}_D 1.5449; ^{1}H NMR (60 MHz, CCl_4) δ 1.14 (s, 6 H), 1.35 (d, J = 6.8 Hz, 3 H), 2.12 (br s, 2 H), 2.2–2.3 (m, 2 H), 3.0–3.45 (m, 1 H), 5.05 (d, J = 6.8 Hz, 1 H), 7.24 (br s, 5 H); IR (neat) 3040 (w), 2970 (m), 2940 (w), 2880 (w), 1640 (s), 1400 (s), 1225 (m), 1035 (m), 760 (w), 700 (m) cm^{-1}; mass spectrum, calcd for $C_{17}H_{20}O_2$ 256.1462, found 256.1436.

The stereochemistry of this compound was clearly assigned as trans based on ^{1}H NMR data. The methyl group at δ 1.35 compare more favorably with δ 1.12 of C-4 methyl of trans compound A than with δ 0.50 of cis compound B[13a] in which the cis methyl group is shielded by the phenyl group. The coupling constant

(J = 6.8 Hz) between C-4 methine and C-5 methine protons also compared more favorably with J = 8.0 Hz of the trans compound A than with J = 9.2 Hz of the cis compound B.

Adduct of norbornadiene (10): GLC t_R 4.8 min (column A, T = 180 °C); mp 99–102 °C; ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.11 (s, 6 H), 1.55–1.7 (m, 3 H), 2.15–2.3 (m, 4 H), 3.0–3.3 (m, 3 H), 4.83 (d, J = 7.4 Hz, 1 H), 5.8–6.0 (m, 1 H), 6.2–6.4 (m, 1 H); IR (KBr disk) 3070 (w), 2960 (m), 1650 (s), 1630 (s), 1405 (s), 1225 (s), 1150 (s), 1045 (m), 960 (s), 710 (s) cm^{-1}. Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.43; H, 7.97.

2-Pentyl-4-oxo-6,6-dimethyl-2,3,4,5,6,7-hexahydrobenzofuran (11): GLC t_R 5.4 min (column A, T = 180 °C); n^{30}_D 1.4903; ^{1}H NMR (60 MHz, CCl_4) δ 1.11 (s, 6 H), 0.75–1.8 (m, 11 H), 2.0–2.3 (m, 4 H), 2.3–3.1 (m, 2 H), 4.5–5.0 (m, 1 H); IR (neat) 2960 (s), 2935 (s), 2870 (m), 1640 (s), 1405 (m), 1225 (m) cm^{-1}; mass spectrum, calcd for $C_{15}H_{24}O_2$ 236.1777, found 236.1795.

2-Acetyl-4-oxo-6,6-dimethyl-2,3,4,5,6,7-hexahydrobenzofuran (12): GLC t_R 3.2 min (column A, T = 180 °C); n^{30}_D 1.5145; ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.13 (s, 6 H), 2.23 (br s, 5 H), 2.3–2.4 (m, 2 H), 2.8–3.15 (m, 2 H), 5.08 (d of d, J = 10.6, 8.2 Hz, 1 H); IR (neat) 2950 (m), 2870 (w), 1715 (s), 1630 (s), 1400 (s), 1220 (m) cm^{-1}; mass spectrum, calcd for $C_{12}H_{16}O_3$ 208.1099, found 208.1084.

Adduct of dihydrofuran (13): GLC t_R 2.8 min (column A, T = 180 °C); mp 105–106 °C; ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.12 (s, 6 H), 1.9–2.2 (m, 2 H), 2.22 (br s, 2 H), 2.3–2.4 (m, 2 H), 3.4–3.9 (m, 2 H), 3.95–4.35 (m, 1 H), 6.25 (d, J = 6.0 Hz, 1 H); IR (neat) 3000 (w), 2960 (m), 2880 (m), 1635 (s), 1410 (s), 1225 (m), 1080 (m), 885 (s). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.51; H, 7.97.

2-Ethenyl-2-methyl-4-oxo-6,6-dimethyl-2,3,4,5,6,7-hexahydrobenzofuran (14): GLC t_R 4.0 min (column A, T = 150 °C); n^{30}_D 1.5012; ^{1}H NMR (60 MHz, CCl_4) δ 1.10 (s, 6 H), 1.46 (s, 3 H), 2.07 (br s, 2 H), 2.1–2.3 (m, 2 H), 2.55–2.7 (m, 2 H), 4.85–5.3 (m, 2 H), 5.85 (d of d, J = 16.8, 10.0 Hz, 1 H); IR (neat)

3100 (w), 2965 (s), 2880 (m), 1640 (s), 1405 (s), 1240 (s), 1015 (m), 925 (m), 870 (m), 755 (m) cm^{-1}; mass spectrum, calcd for $C_{13}H_{18}O_2$ 206.1306, found 206.1304.

2-(1-Propenyl)-4-oxo-6,6-dimethyl-2,3,4,5,6,7-hexahydrobenzofuran (15): GLC t_R 2.8 min (column A, T = 170 °C); n^{30}_D 1.5143; ^1H NMR (60 MHz, CCl_4) δ 1.10 (s, 6 H), 1.74 (d, J = 5.4 Hz, 3 H), 2.09 (br s, 2 H), 2.1–2.3 (m, 2 H), 2.3–3.1 (m, 2 H), 4.84–5.35 (m, 1 H), 5.5–5.75 (m, 2 H); IR (neat) 2970 (s), 2880 (m), 1635 (s), 1405 (s), 1225 (s), 1045 (m), 975 (m), 920 (m) cm^{-1}; mass spectrum, calcd for $C_{13}H_{18}O_2$ 206.1307, found 206.1335.

2-Ethenyl-2-(4-methyl-3-pentenyl)-4-oxo-6,6-dimethyl-2,3,4,5,6,7-hexahydrobenzofuran (16): GLC t_R 3.7 min (column A, T = 200 °C); n^{30}_D 1.5155; ^1H NMR (60 MHz, $CDCl_3$) δ 1.11 (s, 6 H), 1.58 (br s, 3 H), 1.65 (br s, 3 H), 1.5–2.3 (m, 4 H), 2.09 (br s, 2 H), 2.2–2.3 (m, 2 H), 2.6–2.75 (m, 2 H), 4.85–5.3 (m, 3 H), 5.88 (d of d, J = 17, 10 Hz, 1 H); IR (neat) 2950 (s), 2925 (s), 2870 (w), 1630 (s), 1400 (s), 1235 (m), 1035 (w), 990 (w), 920 (w) cm^{-1}; mass spectrum, calcd for $C_{18}H_{26}O_2$ 274.1931, found 274.1925.

(*E*)-2-(2-(Methoxycarbonyl)ethenyl)-3-methyl-4-oxo-6,6-dimethyl-2,3,4,5,6,7-hexahydrobenzofuran (17a): GLC t_R 21 min (column B, T = 170 °C); ^1H NMR (60 MHz, CCl_4) δ 1.07 (s, 6 H), 1.22 (d, J = 7.0 Hz, 3 H), 2.05 (br s, 2 H), 2.15–2.2 (m, 2 H), 2.45–3.25 (m, 1 H), 3.65 (s, 3 H), 4.67 (t with fine coupling, J = 6.0 Hz, 1 H), 5.85 (d, with fine coupling, J = 16 Hz, 1 H), 6.82 (d of d, J = 16, 6 Hz, 1 H); IR (neat) 2945 (s), 2865 (m), 1775 (m), 1735 (s), 1630 (s), 1400 (s), 1220 (m), 1205 (m) cm^{-1}.

(*Z*)-2-(2-Methoxycarbonyl)ethenyl)-3-methyl-4-oxo-6,6-dimethyl-2,3,4,5,6,7-hexahydrobenzofuran (17b): GLC t_R 27 min (column B, T = 170 °C); ^1H NMR (60 MHz, CCl_4) δ 1.04 (d, J = ca. 7 Hz (one peak of the doublet was under the singlet at 1.12), 3 H), 1.12 (s, 6 H), 2.10 (br s, 2 H), 2.27 (br s, 2 H), 3.05–3.55 (m, 1 H), 3.73 (s, 3 H), 5.05–5.4 (m, 1 H), 6.00 (d with fine coupling, J = 16 Hz, 1 H), 6.93 (d of d, J = 16, 6 Hz, 1 H); IR (neat) 2950 (s), 2870 (m), 1720 (s), 1638 (s), 1399 (s), 1308 (s), 1264 (s), 1218 (s), 1167 (s), 1029 (m) cm^{-1}; mass spectrum of a mixture of **17a** and **17b**, calcd for $C_{15}H_{20}O_4$ 264.1360, found 264.1354.

2-Phenyl-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydrobenzofuran (18): GLC t_R 6.0 min (column A, T = 200 °C); ^1H NMR (60 MHz, CCl_4) δ 1.15 (s, 6 H), 2.37 (br s, 2 H), 2.74 (br s, 2 H), 6.77 (s, 1 H), 7.15–7.7 (m, 5 H); IR (KBr disk) 2950 (w), 2870 (w), 1665 (s), 1440 (m), 1220 (m), 755 (m), 680 (m) cm^{-1}. The spectral data were identical with those of the authentic sample prepared according to Gump's method.[16a]

2-Phenyl-3-methyl-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydrobenzofuran (19): GLC t_R 3.4 min (column B, T = 200 °C); ^1H NMR (200 MHz, $CDCl_3$) δ 1.17 (s, 6 H), 2.39 (s, 2 H), 2.48 (s, 3 H), 2.78 (s, 2 H), 7.25–7.5 (m, 3 H) 7.55–7.7 (m, 2H); IR (neat) 3060 (w), 2960 (s), 2875 (m), 1679 (s), 1670 (s), 1497 (s), 1435 (s), 1428 (s), 1062 (s), 760 (s), 690 (s) cm^{-1}; mass spectrum, calcd for $C_{17}H_{18}O_2$ 254.1305, found 254.1294.

Regiochemistry was clearly assigned as 2-phenyl-3-methyl on the basis of ^1H NMR data. The signal pattern of phenyl protons (7.25–7.5 (m, 3 H) and 7.55–7.7 (m, 2 H)) compared more favorably with that of 2-phenylfuran (7.15–7.5 (m, 3 H) and 7.5–7.75 (m, 2 H)) than that of 3-phenylfuran (7.1–7.55 (m, 5 H)).[26]

2-Hexyl-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydrobenzofuran (20): GLC t_R 3 min (column A, T = 200 °C); n^{30}_D 1.4971; ^1H NMR (60 MHz, CCl_4) δ 1.13 (s, 6 H), 0.8–2.0 (m, 11 H), 2.23 (br s, 2 H), 2.51 (br s, 2 H), 2.2–2.55 (m, 2 H), 6.17 (s, 1 H); IR (neat) 2960 (s), 2930 (s), 2870 (m), 1678 (s), 1640 (m), 1585 (w), 1447 (m), 1393 (m), 1230 (m), 1115 (w), 1035 (w) cm^{-1}; mass spectrum, calcd for $C_{14}H_{24}O_2$ 248.1775, found 248.1775.

Copper(I) Bromide. Copper powder (948 mg, 14.9 mmol) was allowed to react with iodine (24 mg, 0.19 mmol) in 5.0 mL of benzene at room temperature until the color of iodine disappeared. Styrene (606 mg, 5.8 mmol) and 2,2-dibromo-5,5-dimethyl-1,3-cyclohexanedione (2.29 g, 7.7 mmol) were added, and the mixture was stirred at 70 °C for 4 h. After having been cooled to room temperature, the reaction mixture was filtered. The solid material was washed with benzene (3 × 5 mL) and dried under vacuum. Pale yellowish green powder (2.04 g, 95% yield based on copper powder) was identified as copper(I) bromide by comparison of its x-ray powder data.

Copper(II) Bromide–Me_2SO Complex. Copper powder (98 mg, 1.6 mmol), styrene (273 mg, 2.6 mmol), and 2,2-dibromo-5,5-dimethyl-1,3-cyclohexanedione (573 mg, 1.9 mmol) were allowed to react in 2.0 mL of Me_2SO at 30 °C for 4 h. Benzene (100 mL) was added to the reaction mixture, and the resulting solid material was separated by filtration, washed with ether (2 × 5 mL), and dried under vacuum. The yellow powder obtained (585 mg, 99% yield based on copper powder) was identified as copper(II) bromide-Me_2SO complex by comparison of its IR spectrum with that of an authentic sample.[8]

Competitive Reactions. The cycloaddition reaction was carried out with styrene and a substituted styrene (1.0 mmol in all), 2,2-dibromo-1,3-cyclohexanedione (0.3 mmol), and copper powder (2.0 mmol, activated by 0.05 mmol of iodine) in 1.0 mL of benzene in a similar fashion as described for the reaction with a single olefin. After the reaction at 70 °C for 1 h, yields of the dihydrofuran derivatives were determined by GLC analysis. The yields based on the olefins were less than 10% under the experimental conditions. Thus the relative reactivity of the substituted styrene was calculated by the equation $k_X/k_H = (P_X/P_H)(O_H/O_X)$, where P_X/P_H is the molar ratio of the dihydrofuran derivatives derived from the substituted styrene and styrene and O_H/O_X is the molar ratio of added styrene and the substituted styrene.[27] The plot of log k_X/k_H against the Hammett σ value is shown in Figure 1.

Reaction of Dibromoacetoacetate, Styrene, and Copper. Dibromoacetoacetate (933 mg, 3.24 mmol), styrene (205 mg, 1.97 mmol), and copper powder (240 mg, 3.78 mmol) were allowed to react in 2.0 mL of Me_2SO at 25 °C for 4 h. The reaction mixture was partitioned between ether and water. GLC analysis of the organic phase indicated the formation of (*Z*)-1-acetyl-1-(ethoxycarbonyl)-2-phenylcyclopropane (30% yield based on styrene), (*E*)-1-acetyl-1-(ethoxycarbonyl)-2-phenylcyclopropane (13%), and 1-methyl-2-(ethoxycarbonyl)-5-phenyl-4,5-dihydrofuran (8%).

(*Z*)-1-Acetyl-1-(ethoxycarbonyl)-2-phenylcyclopropane (21a): GLC t_R 2.8 min (column A, T = 180 °C); ^1H NMR (60 MHz, CCl_4) δ 0.80 (t, J = 7.2 Hz, 3 H), 1.60 (d of d, J = 8.5, 4.4 Hz, 1 H), 2.10 (d, of d, J = 8.5, 4.4 Hz, 1 H), 2.38 (s, 3 H), 3.17 (t, J = 8.5 Hz, 1 H), 3.80 (q, J = 7.2 Hz, 2 H), 7.14 (br s, 5 H); IR (neat) 2995 (m), 1730 (s), 1700 (s), 1380 (m), 1325 (m), 1265 (m), 1185 (m), 1130 (m), 700 (m) cm^{-1}.

(*E*)-1-Acetyl-1-(ethoxycarbonyl)-2-phenylcyclopropane (21b): GLC t_R 3.4 min (column A, T = 180 °C); ^1H NMR (60 MHz, CCl_4) δ 1.31 (t, J = 7.2 Hz, 3 H), 1.5–1.7 (m, 1 H), 1.82 (s, 3 H), 2.1–2.4 (m, 1 H), 3.12 (t, J = 8.6 Hz, 1 H), 4.20 (q, J = 7.2 Hz, 2 H), 6.95–7.25 (m, 5 H); IR (neat) 2990 (m), 1735 (s), 1710 (s), 1280 (s), 1185 (m), 1125 (m), 700 (m) cm^{-1}; mass spectrum of a mixture of **21a** and **21b**, calcd for $C_{14}H_{16}O_3$ 232.1099, found 232.1107.

2-Methyl-3-(ethoxycarbonyl)-5-phenyl-4,5-dihydrofuran (22): GLC t_R 5.4 min (column A, T = 180 °C); ^1H NMR (60 MHz, CCl_4) δ 1.26 (t, J = 7.2 Hz, 3 H), 2.25 (t, J = 1.6 Hz, 3 H), 2.6–3.55 (m, 2 H), 4.10 (q, J = 7.2 Hz, 2 H), 5.50 (d of d, J = 10.4, 9.2 Hz, 1 H), 7.26 (br s, 5 H); IR (neat) 3070 (w), 3040 (w), 2980 (m), 2940 (m), 2880 (w), 1700 (s), 1655 (s), 1230 (s), 1085 (s), 975 (s), 760 (m), 700 (m) cm^{-1}.

This compound has also been reported by Barreau et al.[28] The ^1H NMR spectrum was identical within an experimental error.

Attempt To Isomerize 1-Acetyl-1-(ethoxycarbonyl)-2-phenylcyclopropane to 1-Methyl-2-(ethoxycarbonyl)-5-phenyl-4,5-dihydrofuran. A mixture of 1-acetyl-1-(ethoxycarbonyl)-2-phenylcyclopropane (Z/E = 63/37) (20.3 mg, 0.087 mmol), copper (72 mg, 1.13 mmol), Cu_2Br_2 (143 mg, 0.498 mmol), and Me_2SO (1.0 mL) was stirred at room temperature for 24 h. No appreciable change was observed by GLC. Then Cu_2Br_2 (76.5 mg, 0.267 mmol) and $CuBr_2$ (115 mg, 0.514 mmol) were added, and the mixture was stirred at room temperature. After 2 days, GLC analysis indicated that no isomerization of the cyclopropanes to the dihydrofuran derivative took place.

2-(Phenylthio)-3-methyl-4-oxo-6-methyl-2,3,4,5,6,7-hexahydrobenzofuran (23). 2,2-Dibromo-5-methyl-1,3-cyclo-

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hexanedione (429 mg, 1.70 mmol) was allowed to react with copper (197 mg, 3.10 mmol) activated with 8.6 mg of iodine and 1-(phenylthio)-1-propene (161 mg, 1.07 mmol) in refluxing benzene for 2 h. After the usual workup, flash chromatography (9:1 hexane/ethyl acetate) gave three fractions containing the title compound; (1) 56 mg (*E* isomer), (2) 31 mg (a 1:1 mixture of *E* and *Z* isomers), and (3) 38 mg (*Z* isomer). Total yield was 43% (*E*/*Z* = 56/44).

***E* isomer**: TLC (4:1 hexane/ethyl acetate) R_f 0.22; ^{1}H NMR (60 MHz, CCl_4) δ 1.0–1.3 (m, 3 H), 1.30 (d, *J* = 6 Hz, 3 H), 1.8–2.6 (m, 5 H), 2.8–3.7 (m, 1 H), 5.5 (d, *J* = 5 Hz, 1 H), 7.1–7.6 (m, 5 H), IR (neat) 3050 (w), 2950 (m), 2920 (w), 2860 (w), 1635 (s), 1395 (s), 1205 (s), 1020 (m), 885 (m), 735 (m), 635 (m) cm^{-1}.

***Z* isomer**: TLC (4:1 hexane/ethyl acetate) R_f 0.18; ^{1}H NMR (60 MHz, CCl_4) δ 0.9–1.3 (m, 3 H), 1.35 (d, *J* = 7 Hz, 3 H), 1.7–2.7 (m, 5 H), 3.2–3.8 (m, 1 H), 6.1 (d, *J* = 9 Hz, 1 H), 7.2–7.7 (m, 5 H); IR (neat) 3050 (w), 2950 (m), 2925 (m), 2860 (w), 1640 (s), 1390 (m), 1200 (m), 1020 (m) cm^{-1}.

The spectral data of both isomers of **23** are very similar to those reported in the literature,[17] except for NMR signals of the 6-methyl group. Presumably our compounds are mixtures of stereoisomers as far as the 6-methyl group is concerned, whereas the compounds reported in the literature seem to be isomerically pure.

Registry No. **1**, 92912-81-7; **2**, 92898-22-1; **3**, 92898-23-2; **4**, 13463-61-1; **5**, 92912-82-8; **6**, 97467-11-3; **7**, 97467-12-4; **8**, 97467-13-5; **9**, 92898-24-3; **10**, 97467-14-6; **11**, 92898-18-5; **12**, 97467-15-7; **13**, 97467-16-8; **14**, 92898-19-6; **15**, 92898-20-9; **16**, 97485-96-6; **17**, 97467-17-9; **18**, 18150-87-3; **19**, 97467-18-0; **20**, 92898-21-0; **21a**, 92898-25-4; **21b**, 92898-26-5; **22**, 54023-37-9; **23**, 67808-96-2; $C_6H_5C(CH_3)=CH_2$, 98-83-9; *p*-$CH_3C_6H_4CH=CH_2$, 622-97-9; *p*-$ClC_6H_4CH=CH_2$, 1073-67-2; *m*-$CF_3C_6H_4CH=CH_2$, 402-24-4; (*Z*)-PhCH=$CHCH_3$, 766-90-5; (*E*)-PhCH=$CHCH_3$, 873-66-5; $C_5H_{11}CH=CH_2$, 592-76-7; $CH_3COCH=CH_2$, 78-94-4; $CH_2=C(CH_3)CH=CH_2$, 78-79-5; $CH_2=CHCH=CHCH_3$, 504-60-9; $CH_2=CHC(=CH_2)CH_2CH_2CH=C(CH_3)CH_3$, 123-35-3; $CH_3CH=CHCH=CHCOOMe$, 1515-80-6; PhC≡CH, 536-74-3; PhC≡CCH_3, 673-32-5; $C_6H_{13}C≡CH$, 629-05-0; 3,3-dibromo-2,4-pentanedione, 4111-99-3; acetylacetone, 123-54-6; 2,2-dibromo-1-phenyl-1,3-butanedione, 97467-19-1; 1-phenyl-1,3-butanedione, 93-91-4; copper, 7440-50-8; 2,2-dibromo-1,3-cyclohexanedione, 6648-30-2; styrene, 100-42-5; cuprous bromide, 7787-70-4; cupric bromide, 7789-45-9; ethyl 2,2-dibromoacetoacetate, 89415-67-8; 2,2-dibromo-5-methyl-1,3-cyclohexanedione, 21544-85-4; 1-(phenylthio)-1-propene, 22103-05-5; 2,2-dibromo-5,5-dimethyl-1,3-cyclohexanedione, 21428-65-9; 2,5-norbornadiene, 121-46-0; 2,3-dihydrofuran, 1191-99-7.

Stereochemistry of the Reductive Alkylation of α,β-Epoxy Ketones

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α-Epoxy ketones have been found to be useful intermediates for the regiospecific alkylation of ketones. We have examined the steric course of the alkylation and shown it to be highly stereoselective.

Regio- and stereoselective formation of new carbon–carbon bonds is a fundamental problem in synthetic organic chemistry. One of the more important bond-forming reactions is the alkylation of carbonyl-activated carbons. However, when an unsymmetrical ketone with protons at both the α and α′ positions is treated with a base, two enolates are possible. Usually a mixture of enolates is formed; the composition of the mixture being dependent upon the conditions used in proton abstraction. D'Angelo has reviewed ways in which regiospecific enolates may be prepared.[1] One useful approach is the direct generation of specific enolates by treatment of ketones with dissolving metals in liquid ammonia or with organometallic reagents under appropriate conditions. Many of the applications of this approach have been tabulated.[2] This method is, of course, limited to those cases which involve α,β-unsaturated ketones or ketones with appropriate α-substitution (leaving groups).

With respect to enolate alkylations, there are two main factors which influence the stereochemical outcome of the reaction: (1) stereoelectronic control and (2) steric hindrance to the approach of the alkylating agent. Stereoelectronic control dictates that the alkylating agent approach the plane of the enolate in a perpendicular manner, allowing maximum orbital overlap during bond formation and bond cleavage. Steric hindrance considerations dictate that the alkylating agent approach the enolate from the most accessible face.

House[3] and Jackman and Lange[4] have summarized much of the work on stereochemistry of alkylation. Despite the variance of results, two observations seem generally applicable: first, the presence of an α-substituent such as an alkyl, cyano, or carbalkoxy group enhances the degree to which alkylation at that carbon proceeds via the axial mode. Second, if axial alkylation results in a 1,3-diaxial interaction, the product from equatorial alkylation is frequently favored.

The reaction mechanism which best explains the stereochemical outcome of enolate alkylations has been suggested by Lansbury[5] and House.[6] In this mechanism it is suggested that the enolate oxygen and the α R group do not remain coplanar after enolate formation. Instead, they become staggered (at a dihedral angle of θ) so as to diminish any eclipsing interaction. Approach of the enolate via the path which leads to axial alkylation tends to

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