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Reaction of α,α'-Dibromo Ketones and Iron Carbonyls. Mechanistic Aspects[1,2]

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Abstract: The mechanism of the title reaction has been examined with various substrates and reaction conditions. Reaction of *endo*-α-bromocamphor with Fe₂(CO)₉ in *N,N*-dimethylformamide (DMF) containing 5% of D₂O affords *exo*-α-deuterio-camphor in 80% yield. Debromination of 2,4-dibromo-2,4-dimethylpentan-3-one with Fe₂(CO)₉ in moist DMF proceeds in a stepwise manner, giving first 2-bromo-2,4-dimethylpentan-3-one and then 2,4-dimethylpentan-3-one. Treatment of 1,3-dibromo-1,3-diphenylpropan-2-one with Fe₂(CO)₉ in benzene produces 1-phenyl-2-indanone in 70% yield. Reductive rearrangement of 2,4-dibromo-6,6-diphenylbicyclo[3.1.0]hexan-3-one affords 6,6-diphenylbicyclo[3.1.0]hex-3-en-2-one in 95% yield. Reaction of 3,5-dibromo-2,2,6,6-tetramethylheptan-4-one gives a cyclization product, 2-*tert*-butyl-3,3,4-trimethylcyclobutanone, in 78% yield. Reduction of 2,6-dibromo-2,6-di-*tert*-butylcyclohexanone in benzene gives a mixture of 5-*tert*-butyl-1,7,7-trimethylbicyclo[3.2.0]heptan-6-one (80%), 2-*tert*-butyl-6-isopropyl-6-methylcyclohex-2-enone (3%), and 2,6-di-*tert*-butylcyclohex-2-enone (15%). In DMF or tetrahydrofuran (THF), the di-*tert*-butylcyclohexenone is the sole isolable product. 2,6-Dibromo-2,6-diisopropylcyclohexanone upon reaction with Fe₂(CO)₉ in methanol gives 2-methoxy-2,6-diisopropylcyclohexanone (two stereoisomers, 61% yield) along with 2,6-diisopropylcyclohex-2-enone (21%). Reaction of 2,4-dibromo-2,4-dimethylpentan-3-one in the presence of sodium acetate gives 2-acetoxy-2,4-dimethylpentan-3-one (60%) and 2,4-dimethylpent-1-en-3-one (20%). Regioselectivity has been observed in the reaction of an unsymmetrical dibromo ketone. Treatment of 2,4-dibromo-2-methylpentan-3-one with Fe₂(CO)₉ in methanol gives two kinds of methoxy ketones, 2-methoxy-2-methylpentan-3-one and 2-methoxy-4-methylpentan-3-one, in a ratio of 90:10 (45% combined yield); the reduction in DMF containing sodium acetate gives rise to 2-acetoxy-2-methylpentan-3-one and 2-acetoxy-4-methylpentan-3-one in a 69:31 ratio (46% yield) accompanied by a small amount of 2-methylpent-1-en-3-one (<3%) and 2-methylpentan-3-one (9%). These findings indicate that the reaction of dibromo ketones with iron carbonyls produces first enolate intermediates and subsequently reactive oxyallyl–iron(II) species. The latter species, depending on their structures and reaction conditions, experience a variety of cationic rearrangements, nucleophilic trapping, and prototropy forming α,β-unsaturated ketones, etc.

Organic reactions of α-halo ketones have received considerable attention in recent years and proved to be of great synthetic value. The diversity of the chemical reaction is ascribed

to the presence of various functionalities in the molecules, viz., reactive halogen–carbon bond, acidic hydrogen atom, and carbonyl moiety. The halogen atom suffers facile nucleophilic

displacement or reduction giving the parent ketones.[5] Treatment with basic reagents causes a variety of transformations such as dehydrohalogenation producing α,β-unsaturated ketones,[6] displacement,[7] epoxide formation,[8] Favorskii rearrangement,[9] semibenzilic acid rearrangement,[10] etc., depending on the nature of the reagents and substrates. Alkylation of α-halo ketones can be effected by the Reformatsky-type reaction[11] or by the use of a combination of trialkylboranes and sterically hindered alkoxides.[12] The reaction with nickel carbonyl[13] or iron carbonyl[14] leads to the dimeric coupling products, the reaction course being highly dependent on the reaction conditions.

α,α'-Dihalo ketones are also useful in organic synthesis. For example, the double dehydrohalogenation reaction with tertiary amines gives rise to cyclopropenone derivatives.[15] In certain cases α,α'-dihalo ketones behave as α-monohalo ketones do. Some reactions, however, are unique to the dihalo ketone structure. Particularly interesting is their behavior displayed in the presence of various reducing agents. The gas-phase reaction of the dihalo ketone 1 (R, R' = H, CH₃, etc.; X = Cl, Br) with potassium vapor produces carbon monoxide and an olefin of type RR'C=CRR'.[16] The halogen atoms are smoothly removed by electroreduction in polar aprotic solvents as well.[17] Reduction of dibrominated dibenzyl ketone (1, R = C₆H₅; R' = H; X = Br) with sodium iodide in aprotic media leads to the dimeric products 2 and 3 (R =
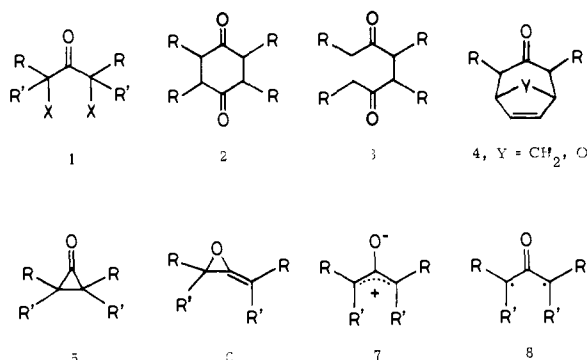

C₆H₅),[18,19] while the reaction in the presence of cyclopentadiene or furan gives the bicyclic ketone 4 (R = C₆H₅) in high yield.[18] The latter cyclocoupling reaction is also possible with the aid of zinc dust,[18] zinc–copper couple,[20] copper–isonitrile complexes,[21] copper–sodium iodide,[20] etc. Reductive alkylation of the dihalo ketones with organocuprate reagents[22] or trialkylboranes[23] is also important from a synthetic point of view. Various species have been postulated as the reactive intermediate which experiences such intermolecular reactions. The isomeric structures, cyclopropanone 5, allene oxide 6, 2-oxyallyl dipolar ion 7, and 2-oxo-1,3-alkadiyl diradical 8, could all account for the observations.

In a continuing effort to develop new methods to construct carbocyclic frameworks with the aid of transition metal complexes, we have studied the reduction of α,α'-dibromo ketones with iron carbonyls and found that the reaction proceeds via the mechanism outlined in Scheme I.[2] Initially, the iron enolate 10 is formed by either two-electron reduction of the dibromo ketone 9 with an iron carbonyl or oxidative addition of the carbon–bromine bond of 9 onto zerovalent iron atom[14] followed by the change into the more stable structure. The second step is an S_N1-type or ferrous ion assisted elimination of the allylic bromine atom to produce the reactive oxyallyl species 11. In this paper we present chemical evidence for this scheme.
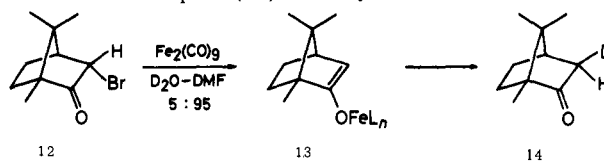
Results and Discussion

Evidence for the Formation of Iron Enolate Species. Reaction of α-Bromo Ketones with Fe₂(CO)₉ in the Presence of Water.

Scheme I
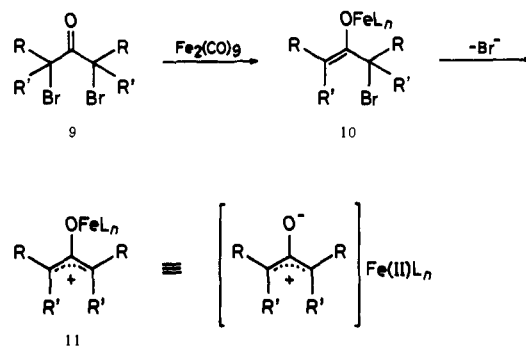
L = Br, CO, solvent, etc.

Reaction of *endo-α*-bromocamphor (12) with Fe₂(CO)₉ in DMF in the presence of 5% of deuterium oxide afforded monodeuteriocamphor (14) in 80% yield. The stereochemistry


of the deuterium atom was assigned as exo by examination of the NMR spectrum.[24] Protonation toward enol or enolate of camphor is known to occur from the exo side of the bicyclic system,[24,25] and hence the present stereoselective reduction indicates the presence of the iron enolate 13 as the reactive intermediate.[13,14,26]

α,α'-Dibromo ketones can also be debrominated smoothly by Fe₂(CO)₉. Reduction of dibromo ketones with 0.5 equiv of Fe₂(CO)₉ was carried out in a mixture of H₂O and DMF (5:95) at 25 °C and the reaction course was monitored by GLC. The yield of the corresponding monobromide reached maximum after several hours and then decreased, while that of parent ketone increased steadily during the reaction. This fact reveals that the reduction proceeds in a stepwise manner, producing first the monobromide and subsequently the completely reduced ketone. These reactions can be most reasonably interpreted by intervention of an iron enolate intermediate at each reaction step.

Evidence for the Formation of Oxyallyl–Fe(II) Intermediate 11. A. Reductive Rearrangements of α,α'-Dibromo Ketones with Fe₂(CO)₉. The following four skeletal changes provide definite evidence that the initially formed enolate 10 suffers further elimination of bromide ion to give oxyallyl–Fe(II) species 11 (Scheme I).

(a) Reaction of 1,3-Dibromo-1,3-diphenylpropan-2-one (15). Electrocyclization of 1,3-Diphenyl-2-oxyallyl Cation (16). Reduction of the dibromo ketone 15 with Fe₂(CO)₉ in benzene at 25 °C gave rise to 1-phenyl-2-indanone (18)[27] in 70% yield. This reaction is best explained by assuming the intervention
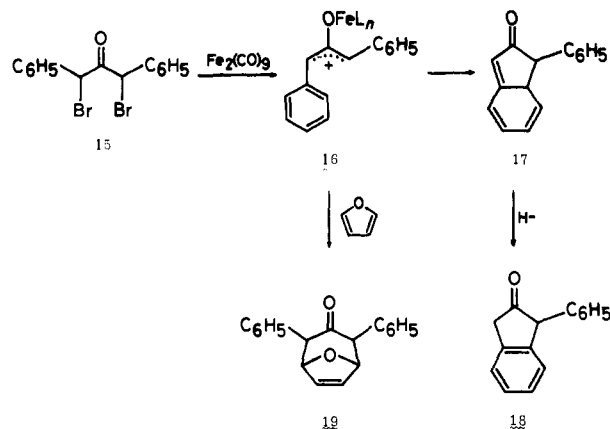
of the oxyallyl–Fe(II) complex **16**. Conrotatory electrocyclization of the pentadienyl cation (a 4π-electron system)[28] or intramolecular electrophilic attack of the allyl cation to the aromatic ring gives **17**, which in turn undergoes aromatization to yield the indanone **18**. Similar cyclization of 1-phenylallyl cations to indenes is well known.[29]

When the reaction was carried out in a mixture of benzene and furan (1:1.5 v/v), the indanone derivative **18** could not be obtained, but instead the bicyclic adduct **19** was formed in 90% yield (a 1:1 mixture of cis and trans isomers).[30] The adduct resulted from the intermolecular [$_\pi 2 + _\pi 4$] cycloaddition of the oxyallyl intermediate **16** and furan.[18,31]

(b) Reduction of 2,4-Dibromo-6,6-diphenylbicyclo[3.1.0]-hexan-3-one (20). [$1_a,4_s$] Sigmatropic or [$_\sigma 2_s + _\sigma 2_s + _\pi 2_s$] Dyotropic Rearrangement of the Oxyallyl Cation 21. Reaction of **20** and $Fe_2(CO)_9$ in benzene or DMF at 25 °C afforded the
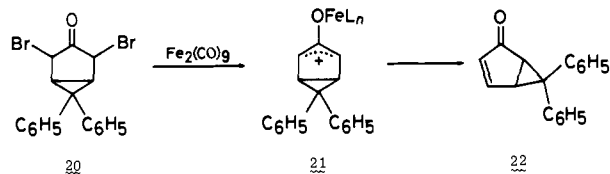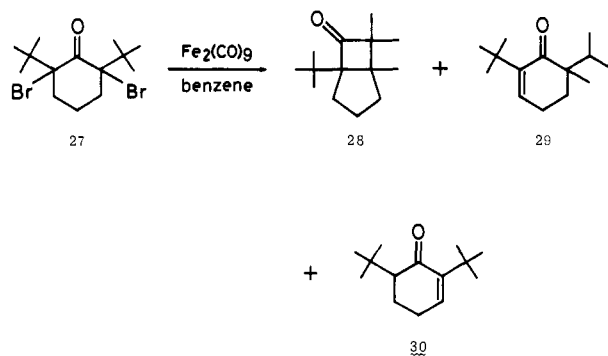

bicyclic cyclopentenone derivative **22** in 95% yield. The product was identified by comparison with an authentic sample.[32] This type of skeletal change is known and explained by a cationic [$1_a,4_s$] sigmatropic rearrangement[33,34] (or a [$_\sigma 2_s + _\sigma 2_s + _\pi 2_s$] dyotropic rearrangement according to the definition of Reetz)[34] of the oxyallyl–Fe(II) species **21**.

(c) Reduction of 3,5-Dibromo-2,2,6,6-tetramethylheptan-4-one (23) with $Fe_2(CO)_9$. Neopentyl Rearrangement of 1,3-Di-*tert*-butyl-2-oxyallyl Cation (24). With the expectation that the cation **24**, if formed, should undergo the well-known neopentyl-type rearrangement,[35,36] reduction of the dibromo ketone **23** with $Fe_2(CO)_9$ was carried out in benzene. After usual
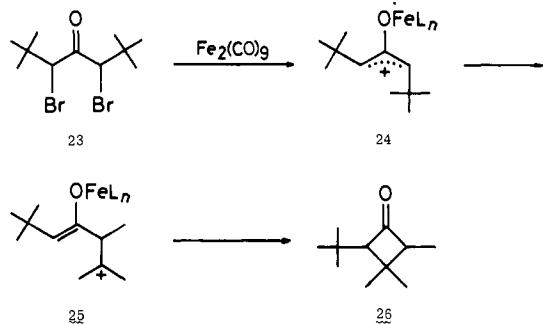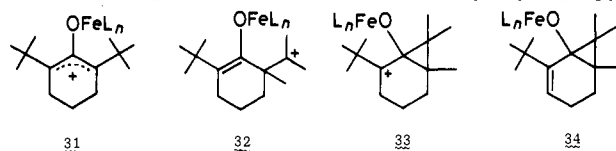

workup, the cyclobutanone **26** was obtained in 78% yield as a ca. 5:1 mixture of cis and trans isomers, stereochemistry being established by Eu(fod)$_3$-aided NMR analysis. Apparently, the products result from 1,2-methyl shift of the oxyallyl **24** followed by ring closure of the zwitterion **25**.

(d) Reaction of 2,6-Dibromo-2,6-di-*tert*-butylcyclohexanone (27). *tert*-Butylallyl–Cyclopropylcarbinyl Rearrangement. Reduction of **27** with $Fe_2(CO)_9$ in benzene at 25 °C gave rise to three products, **28**, **29**, and **30**, in 80, 3, and 15% yields, re-

spectively. The reaction in DMF or THF gave no rearrangement product, but afforded **30** in high yield.

The formation of the products **28–30** can be best explained by the mechanism through oxyallyl **31**. The initial 1,2-methyl shift, affording **32**, followed by the homoallyl–cyclopropyl-

carbinyl rearrangement[37,38] produces **33**. The cyclopropyl-carbinyl–cyclobutonium transformation with the aid of the electron-releasing oxygen atom gives rise to the final cyclobutanone product **28**. The enone **29** is formed by the deprotonation followed by opening of the cyclopropane ring (**33** → **34** → **29**). The product **30** is formed directly from **31** by prototropy. In basic media such as DMF or THF, this pathway becomes exclusive. Both **24** and **31** are oxyallyl species which have two *tert*-butyl groups at the terminal positions. However, the former is assumed to have sickle configuration, whereas the geometry of the latter is constrained to be W-form. Therefore the reactions of zwitterions **25** and **32** resulting from their 1,2-methyl shift are forced to follow different pathways.

B. Trapping of the Oxyallyl Intermediates with Nucleophiles. The intermediacy of oxyallyl species in the reduction of α,α'-dibromo ketones with $Fe_2(CO)_9$ was corroborated by trapping the reactive species with some nucleophiles as well. In spite of the presence of nucleophiles, the Favorskii reaction expected from the possible cyclopropanone intermediates did not occur. Products arising from nucleophilic attack on the carbonyl carbon of the cyclopropanones were not derived either.

(a) Reaction of 2,6-Dibromo-2,6-diisopropylcyclohexanone (35) in Methanol. The dibromo ketone **35** has a structure similar to **27**. The isopropyl derivative, however, no longer causes the skeletal changes upon interaction with $Fe_2(CO)_9$. The reactions in benzene, DMF, and THF all led to the cyclohexenone derivative **36**. Here collapse of an oxyallyl species by
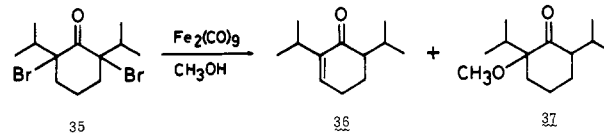
prototropy is apparent. On the other hand, when the reaction was carried out in methanol, the methoxy ketone **37** (cis:trans = 69:31) was obtained in 61% yield along with the enone **36** (21%). The stereochemistry of the methoxy ketones could be easily verified by the NMR analysis.[39]

(b) Reaction of 2,4-Dibromo-2,4-dimethylpentan-3-one (38) in the Presence of Sodium Acetate. Reduction of the dibromide **38** with $Fe_2(CO)_9$ in dry DMF at 30 °C containing a large
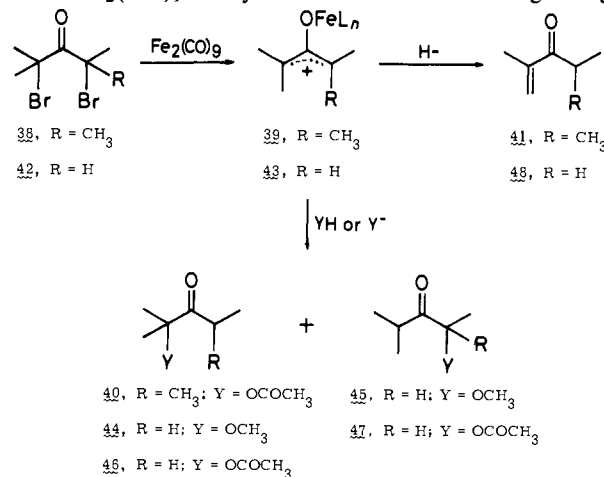
excess of sodium acetate afforded a mixture of the acetoxy ketone **40** (60%) and the enone **41** (20%). Initial formation of the oxyallyl cation **39** followed by its reaction with acetate ion gives **40**, while hydrogen reorganization gives rise to the enone **41**. In the absence of sodium acetate there was obtained a mixture of **41** (80%) and the parent ketone (9%).

(c) Regioselectivity in the Nucleophilic Trapping of Unsymmetrical Oxyallyl Species. A marked regioselectivity was observed in the iron carbonyl promoted reaction of nucleophiles and unsymmetrically substituted dibromo ketones.[40] For instance, the reaction of 2,4-dibromo-2-methylpentan-3-one (**42**) with Fe$_2$(CO)$_9$ in methanol gave regioisomeric methoxy ketones **44** and **45**[41] (45% combined yield) in a ratio of 90:10. A small amount (<3%) of 2-methylpentan-3-one was produced. Enones were not detected in the reaction mixture.

In the reaction with sodium acetate as a nucleophile, a similar regioselectivity was observed. The reaction in the presence of fivefold excess of sodium acetate gave **46** and **47** (46% combined yield) in a ratio of 69:31 accompanied by a small amount (<3%) of the enone **48**. The preferential attack of the nucleophile at the more substituted sp^2 terminus of the unsymmetrical oxyallyl **43** is reasonably understood in view of the greater coefficient of the lowest unoccupied molecular orbital compared with that of the less substituted terminus.[40]

Nature of the Reaction Intermediates. Reduction of α,α'-dibromo ketone **9** with iron carbonyls has proved to produce in the first place the enolate **10**. Various three-carbon units could be considered a priori as the reactive species further generated therefrom. The three-membered ring **5** or **6**, or the open form **7** or **8**, might serve as the possible candidate. The foregoing skeletal rearrangements and reactions with nucleophiles as well as prototropy giving enones provide definite evidence for the occurrence of oxyallyl–Fe(II) species **11** as the *product-determining intermediates*. Any other reactive species can explain the above findings only partly. Certain cyclopropanones **5**[42] and allene oxides **6**[43] have been synthesized and characterized. Based on their chemical properties, it is inconceivable that these neutral substances undergo directly the observed cationic reactions. Rather, these molecules are kinetically labile and, even if formed by the present reaction, interact immediately with ferrous bromide present in the reaction system to result in the formation of **11** that displays the eminent cationic behavior.[44] 2-Oxyallyl species of type **7** is formally a dipolar ion. In the present reaction intermediate **11**, however, the negative charge on the oxygen atom is masked by binding to ferrous ion. Consequently, the reactive species can behave as a simple allylic cation bearing an oxygen function at the central sp^2 carbon atom. It remains still unclear what kind of interaction exists between the allylic moiety and Fe(II) ion, but, since no stable allyl cation–Fe(II) complexes have been isolated, π-type interaction seems unlikely to be present. In any event, the chemical behavior can be explained economically without considering such complicated perturbations.

Dibromo ketones having long alkyls generally undergo reactions characteristic of oxyallyl species.[30,45] α,α'-Dibromoacetone, however, does not give the products arising from the oxyallyl intermediate. The failure is not so surprising in view of the mechanism of Scheme I. Reduction of dibromoacetone with iron carbonyl first forms the unstable,[46] highly reactive enolate **10** (R = R' = H), which in turn has to lead to the quite unstable oxyallyl intermediate **11** (R = R' = H) bearing no carbocation-stabilizing substituents at the cationic termini.[47] In order to achieve the reaction of oxyallyl species effectively, therefore, the reactivity and stability of these intermediates must be appropriately controlled by steric and electronic effects of substituents.

Intermediacy of an analogous oxyallyl species has been

suggested for the reaction of dibromo ketones with Zn or zinc–copper couple.[18,20] In fact, the reaction of **20** with zinc-copper couple causes the same rearrangement to give **22**.[33] Furthermore, treatment of certain dibromo ketones with the same reducing agent in methanol affords the corresponding α-methoxy ketones as well.[41] It should be added, however, that the reaction with certain substrates follows different pathways. For instance, the zinc reduction of **15** does not produce the indanone **18** but instead gives the dimeric products **2** and **3** (R = C$_6$H$_5$).[19] Another remarkable contrast was observed with the behavior of the dibromide **27**, affording, in addition to **28** (11%) and **30** (28%), three new products, **49** (40%), **50** (3%),

49　　　50　　　51
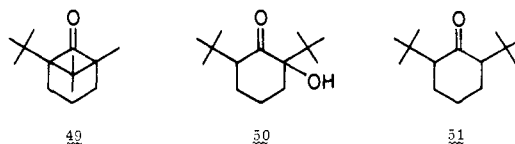
and **51** (4%).[48] Particularly interesting is the formation of **49**. Reaction of **27** and nickel carbonyl, like the reduction with Fe$_2$(CO)$_9$, yielded the bicyclic ketone **28** (5%) and the enone **30** (64%). The exact origin of the observed differences in the reaction modes has not been elucidated yet but probably is associated with the stabilities and reactivities of the oxyallyl and the precursory enolates. Difference in the reducing ability of the metals as well as the nature of bonding between the metal ions and oxygen atom (ionic or covalent) in the intermediates may be responsible for the alternation of the reaction course.

Conclusion

The reaction of α,α'-dibromo ketones with iron carbonyls proceeds by the mechanism outlined in Scheme I. The oxyallyl–Fe(II) intermediates suffer various cationic rearrangements depending on the structure, nucleophilic trapping, and prototropy to form α,β-unsaturated ketones. The reactive three-carbon unit is highly useful for the preparation of odd-numbered carbocycles. The subsequent five papers will describe the synthetic utilization of this reaction.

Experimental Section

General. All melting and boiling points are uncorrected. Infrared (IR) spectra were measured on a JASCO Model IR-A-I or JASCO Model DS-402G spectrometer in CCl$_4$ solution unless otherwise noted. Nuclear magnetic resonance (NMR) spectra were determined with either a JEOL Model C-60H or Varian Model HA-100D spectrometer in CCl$_4$ solution unless otherwise stated. Chemical shifts were given in parts per million relative to internal tetramethylsilane standard. Singlet, doublet, triplet, quartet, and multiplet were abbreviated to s, d, t, q, and m, respectively. Mass spectra were obtained with a Hitachi RMU-6C mass spectrometer operating at an ionization energy of 70 eV. Analytical gas–liquid phase chromatography (GLC) was performed on a Hitachi Model 063 or Yanagimoto Model G-8 instrument equipped with a flame ionization detector using nitrogen as carrier gas. Preparative separation was carried out with a Varian Model 1700 gas chromatograph attached with a thermal conductivity detector by use of helium as carrier gas. The following columns were used: A, 2 m × 4 mm 5% poly(ethylene glycol) succinate on 60–80 mesh Celite 545; B, 10 ft × ³/₈ in. 15% Carbowax 20M on 60–80 mesh Celite 545; C, 3 m × 4 mm 15% Carbowax 20M on 60–80 mesh Celite 545; D, 2 m × 3 mm 3% Silicone OV-17 on 60–80 mesh Diasolid L; E, 2 m × 4 mm 12% diisodesyl phthalate on 60–80 mesh Neopak 1A. Analytical thin layer chromatography (TLC) was done with E. Merck GF-254 silica gel plates (0.25 mm). For preparative scale TLC the plate coated with 1.0-mm thickness of E. Merck GF-254 silica gel was used. High-resolution mass spectra were obtained at the Department of Agricultural Chemistry, Nagoya University. Microanalyses were accomplished at the Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University, and Research Laboratory, Fujisawa Pharmaceutical Co., Ltd.

Materials. Fe$_2$(CO)$_9$ was prepared by the method of King[49] and dried over potassium hydroxide in a vacuum desiccator before use.

Zn/Cu couple was obtained according to the procedure reported in the literature.[50] α,α'-Dibromo ketones, **15, 38,** and **42,** were synthesized in the usual manner.[51] Dibromides **20** and **23** were produced according to the methods of Zimmerman[32] and Ciabattoni,[52] respectively. Dibromo ketones were used as obtained and no efforts to separate diastereomers were made. Oily dibromo ketones were purified by passing through a short column packed with basic alumina (Woelm activity I) immediately before use. Benzene and THF were distilled from LiAlH₄ and stored over molecular sieves 3A. DMF was distilled after refluxing over CaH₂ overnight in N₂ atmosphere and stored under N₂. D₂O (99.8%) was supplied from Stohler Isotope Chemicals.

Reduction of α-Bromocamphor (12) with Fe₂(CO)₉ in the Presence of D₂O. A mixture of **12** (230 mg, 1.00 mmol) and Fe₂(CO)₉ (444 mg, 1.20 mmol) in 5:95 D₂O–DMF (2.5 mL) was stirred at 60 °C for 20 h and then was poured into water (5 mL). The aqueous layer was extracted with 1:1 ethyl acetate–hexane (10 mL × 4) and the combined organic layers were dried over Na₂SO₄. Removal of the solvent followed by chromatography on silica gel (1:10 ether–benzene) afforded the deuteriocamphor **14** (121 mg, 80% yield). The ketone **14** was identified by comparison of the NMR spectrum with that of an authentic sample.[24] Mass spectrum indicated that **14** consists of d_0 (13%) and d_1 compounds (87%).

Reduction of 2,4-Dibromo-2,4-dimethylpentan-3-one (38) with Fe₂(CO)₉ in DMF in the Presence of H₂O. A mixture of Fe₂(CO)₉ (745 mg, 2.05 mmol) and **38** (1.08 g, 4.00 mmol) in 5:95 H₂O–DMF (10 mL) was stirred at room temperature for 24 h and then poured into cold water (100 mL) The mixture was extracted with benzene (15 mL × 3) and the combined extracts were washed with water. The benzene solution was analyzed by GLC (column A, 70 °C, diisobutyl ketone as internal standard) indicating that 2-bromo-2,4-dimethylpentan-3-one and 2,4-dimethylpentan-3-one were formed in 15 and 25% yields, respectively. The unreacted dibromide **38** was recovered in 45% yield.

Reaction of 1,3-Dibromo-1,3-diphenylpropan-2-one (15) with Fe₂(CO)₉ in Benzene. A mixture of Fe₂(CO)₉ (5.00 g, 13.7 mmol) and **15** (4.00 g, 10.9 mmol) in dry benzene (50 mL) was stirred at 25 °C for 24 h under N₂. The solid material was removed by filtration through a pad of Celite 545 and the residue was washed with benzene. The combined filtrate and washing were treated with water and the organic layer was dried over Na₂SO₄. The solvent was evaporated to give a viscous oil (1.795 g), which was extracted with hexane. The hexane-soluble materials were chromatographed on silica gel (1:2 benzene–hexane) to give 1-phenyl-2-indanone (**18,** 1.60 g, 70%), mp 50–52 °C (lit.[27] 51–53 °C). The IR, NMR, and mass spectra of **18** were identical with those of an authentic sample prepared from 1-bromo-1,3-diphenylpropan-2-one and AlCl₃.[27] Semicarbazone derived from **18,** mp 197–199 °C (from benzene) (lit.[27] 200–202 °C).

Reaction of 2,4-Dibromo-6,6-diphenylbicyclo[3.1.0]hexan-3-one (20) with Fe₂(CO)₉ in DMF. A mixture of **20** (20 mg, 0.05 mmol) and Fe₂(CO)₉ (22 mg, 0.06 mmol) in dry DMF (0.1 mL) was allowed to stand at 25 °C for 24 h under N₂. The mixture was diluted with 1:1 ethyl acetate–hexane (5 mL) and treated with saturated NaHCO₃ solution (5 mL). The separated organic layer was washed with water and dried over Na₂SO₄. Removal of the solvent left a pale yellow oily residue, which was purified by TLC (1:10 ethyl acetate–hexane), giving 6,6-diphenylbicyclo[3.1.0]hex-3-en-2-one (**22,** 16 mg, 95% yield) as crystals. Upon recrystallization from methanol, an analytical sample of **22,** mp 137–139 °C (lit.[32] 138–140 °C), was obtained. IR, NMR, and mass spectra were superimposable on those of an authentic specimen prepared according to the method of the literature.[32]

Reaction of 3,5-Dibromo-2,2,6,6-tetramethylheptan-4-one (23) with Fe₂(CO)₉ in Benzene. A mixture of **23** (75 mg, 0.23 mmol) and Fe₂(CO)₉ (120 mg, 0.27 mmol) in benzene (1.0 mL) in a 30-mL ampule was heated at 80 °C under N₂. After 6 h, the tube was cooled to −10 °C and opened cautiously (CO pressure!). The mixture was diluted with ether (5 mL). The ether layer was separated, washed with water (5 mL × 4), dried over MgSO₄, and evaporated. Chromatography of the residue (1:10 ethyl acetate–hexane) afforded an oil (50 mg, R_f 0.5), which was further purified by preparative GLC (column B, 130 °C), giving 30 mg (78% yield) of a mixture of *cis*- and *trans*-2-*tert*-butyl-3,3,4-trimethylcyclobutanone (**26**) (retention time (t_R) 17.5 min, 5:1 ratio based on NMR analysis) as a colorless oil. Spectral data of the unseparable mixture follow: IR 1764 cm⁻¹ (C=O); mass spectrum *m/e* 168 (M⁺), 112, 98, 70, 55; exact mass spectrum *m/e* 168.1524 (calcd for C₁₁H₂₀O, 168.1514). NMR of *cis*-**26**: δ 0.97 (d,

J = 7.0 Hz. CHC*H₃*), 1.03 (s, C(CH₃)₃), 1.10 and 1.46 (two s, C(CH₃)₂), 2.72 (m, 2 CH). NMR of *trans*-**26**: δ 1.00 (d, *J* = 7.0 Hz, CHC*H₃*), 1.03 (s, C(CH₃)₃), 1.20 and 1.42 (two s, C(CH₃)₂), 2.72 (m, 2 CH). When the Eu(fod)₃-induced shifts of the major cis isomer were plotted against the relative molar ratio of the shift reagent to the substrate a linear relationship was observed; the gradients, Δppm/mol of Eu(fod)₃ per mol of substrate, of these lines were 2.3 (C(CH₃)₃), 2.2 (CHC*H₃*), and 1.9 and 1.7 (C(CH₃)₂).

Preparation of 2,6-Dibromo-2,6-di-*tert*-butylcyclohexanone (27). To a stirred solution of 2,6-di-*tert*-butylcyclohexanone (**51,** 62 g, 295 mmol) in CHCl₃ (300 mL) was added a solution of Br₂ (94.4 g, 590 mmol) in CHCl₃ (300 mL) at 25 °C over an 8-h period and then the resulting mixture was stirred at the same temperature for 18 h. The mixture was washed with water and the organic layer was dried over MgSO₄. The solvent was removed under reduced pressure, affording a yellow residue which solidified on standing at room temperature. Recrystallization (hexane) gave **27** (15 g, 14% yield) as pale yellow needles: mp 175–177 °C; IR (Nujol) 1710 cm⁻¹ (C=O); NMR (CDCl₃) δ 1.23 (s, 2 C(CH₃)₃), 1.75–2.85 (m, 3 CH₂); mass spectrum *m/e* 370, 368, 366 (1:2:1 ratio, M⁺). Anal. (C₁₄H₂₄OBr₂) C, H.

Reaction of 27 with Fe₂(CO)₉ in Benzene. A mixture of **27** (736 mg, 2.00 mmol) and Fe₂(CO)₉ (728 mg, 2.00 mmol) in benzene (5.0 mL) was stirred at 25 °C under N₂. After 23 h, the mixture was diluted with benzene and the resulting insoluble material was removed by filtration. The filtrate was dried over Na₂SO₄ and concentrated, affording an oily residue. Its GLC analysis (column C, 180 °C, methyl hexanoate as internal standard) showed that 5-*tert*-butyl-1,7,7-trimethylbicyclo[3.2.0] heptan-6-one (**28**) (t_R 12.0 min) was produced in 80% yield accompanied by 2-*tert*-butyl-6-isopropyl-6-methylcyclohex-2-enone (**29**) (t_R 9.2 min, 3% yield) and 2,6-di-*tert*-butylcyclohex-2-enone (**30**) (t_R 8.1 min, 15% yield). Preparative GLC (column B, 180 °C) afforded analytical samples of **28, 29,** and **30.** Spectral and analytical data of the products follow. **28:** IR 1757 cm⁻¹ (C=O); NMR δ 0.98, 1.15, and 1.37 (three s, C(CH₃)₂ and CCH₃), 1.08 (s, C(CH₃)₃), 1.2–2.1 (m, 3 CH₂); mass spectrum *m/e* 208 (M⁺), 193 (M⁺ − CH₃), 180 (M⁺ − CO), 165. Anal. (C₁₄H₂₄O) C, H. The gradients of the lines derived from the Eu(fod)₃-induced spectra were 2.4, 2.2 (C(CH₃)₂), 1.9 (C(CH₃)₃), and 1.6 (CCH₃). **29:** IR 1670 (C=O), 1660 cm⁻¹ (C=C); NMR δ 0.78 and 0.85 (two d, *J* = 7.0 Hz, CH(C*H₃*)₂), 0.89 (s, CCH₃), 1.15 (s, C(CH₃)₃), 1.5–2.0 (m, C*H*(CH₃)₂ and C*H₂*CCH₃), 2.1–2.6 (m, C*H₂*CH=), 6.44 (t, *J* = 4.5 Hz, CH=); mass spectrum *m/e* 208 (M⁺), 193 (M⁺ − CH₃), 180 (M⁺ − CO), 166 (M⁺ − CH₂=CHCH₃), 124; exact mass spectrum *m/e* 208.1844 (calcd for C₁₄H₂₄O, 208.1826). **30** IR 1680 (C=O), 1655 cm⁻¹ (C=C); NMR δ 1.00 (s, CHC(C*H₃*)₃), 1.20 (s, =CC(CH₃)₃), 1.60–2.50 (m, C*H*C(CH₃)₃ and 2 CH₂), 6.38 (m, =CH); mass spectrum *m/e* 208 (M⁺). Anal. (C₁₄H₂₄O) C, H.

Preparation of 2,6-Dibromo-2,6-diisopropylcyclohexanone (35). To a solution of 2,6-diisopropylcyclohexanone (465 mg, 2.55 mmol) in CH₂Cl₂ (3.0 mL) was added a solution of Br₂ (920 mg, 5.75 mmol) in the same solvent (3.0 mL) with stirring at 25 °C over a period of 15 min and the stirring was continued for an additional 30 min. The resulting mixture was diluted with CH₂Cl₂ (10 mL) and washed with water (3 mL). The organic layer was dried over MgSO₄ and concentrated to afford an oily material (1 g). The residue was subjected to bulb-to-bulb distillation, giving **35** (bp 130–140 °C (bath temperature), 0.05 mm, 708 mg, 82% yield) as a pale yellow liquid: IR 1720 cm⁻¹ (C=O); NMR δ 0.98 and 1.16 (two d, *J* = 7.0 Hz, CH(C*H₃*)₂), 1.5–3.0 (m, 3 CH₂ and 2 CH); mass spectrum *m/e* 342, 340, 338 (1:2:1 ratio, M⁺). Anal. (C₁₂H₂₀OBr₂) C, H.

Reaction of 35 and Fe₂(CO)₉ in Methanol. A mixture of Fe₂(CO)₉ (437 mg, 1.20 mmol) and **35** (340 mg, 1.00 mmol) in dry, degassed methanol (8.0 mL) was left with stirring at 25 °C for 24 h under argon. The reaction mixture was evaporated under reduced pressure and the residue was treated with saturated ethylenediaminetetraacetic acid disodium salt (Na₂edta) solution. The aqueous layer was extracted with CH₂Cl₂ (10 mL × 2). The combined organic extracts were washed with water, dried over Na₂SO₄, and concentrated, leaving a pale green oil (208 mg). Preparative TLC (benzene) produced *trans*-2,6-diisopropyl-2-methoxycyclohexanone (**37**) (R_f 0.20, 40 mg, 19% yield) and a 2:1 mixture of *cis*-**37** (42% yield) and 2,6-diisopropylcyclohex-2-enone (**36**) (21% yield) (R_f 0.43–0.63, 126 mg). Analytical samples of *cis*-**37** and **36** were obtained by repeated chromatography (1:40 ether–hexane, R_f 0.4 and 0.5, respectively). **36:** IR (neat film) 1675 (C=O), 1640 cm⁻¹ (C=C); NMR δ 0.85 and 0.92 (two d, *J* = 7.0 Hz, CHCH(C*H₃*)₂), 0.98 (d, *J* = 7.0 Hz,

CCH(CH_3)$_2$), 1.60–2.55 (m, 2 CH$_2$ and C*H*CH(CH$_3$)$_2$), 2.75 (seven-line m, J = 7.0 Hz, ═CCH), 6.49 (t, J = 4.5 Hz, ═CH); exact mass spectrum m/e 180.1510 (calcd for C$_{12}$H$_{20}$O, 180.1514). *cis*-37: IR 1744, 1714 cm^{-1} (C═O); NMR δ 0.65–0.95 (complex m, 2 CH(C*H$_3$*)$_2$), 1.20–3.00 (m, 3 CH$_2$ and 2 CH), 2.97 (s, OCH$_3$); exact mass spectrum m/e 212.1796 (calcd for C$_{13}$H$_{24}$O$_2$, 212.1776). *trans*-37: IR 1720 cm^{-1} (C═O); NMR δ 0.61–0.97 (complex m, 2 CH(C*H$_3$*)$_2$), 1.20–2.95 (m, 3 CH$_2$ and 2 CH), 3.18 (s, OCH$_3$); exact mass spectrum m/e 212.1783 (calcd for C$_{13}$H$_{24}$O$_2$, 212.1776).

Reaction of 2,4-Dibromo-2,4-dimethylpentan-3-one (38) with Fe$_2$(CO)$_9$ in the Presence of Sodium Acetate. A mixture of Fe$_2$(CO)$_9$ (437 mg, 1.20 mmol), 38 (272 mg, 1.00 mmol), and anhydrous sodium acetate (200 mg, 2.47 mmol) in dry DMF (2.5 mL) was stirred at 30 °C for 19 h under N$_2$ and quenched by water (10 mL). The aqueous layer was extracted with 1:1 ethyl acetate–hexane. The combined organic solutions were washed with water and dried over Na$_2$SO$_4$. The GLC analysis (column E, 60 °C) of the organic layer showed that two products were formed. One of them was assigned to 2,4-dimethylpent-1-en-3-one (41) (20% yield based on GLC using 2-methylpentan-3-one as an internal standard) by comparison of the GLC retention time with that of an authentic sample.[10] 2-Acetoxy-2,4-dimethylpentan-3-one (40, 88 mg, 60% yield) was isolated by evaporation of the solvent followed by preparative TLC (1:10 ethyl acetate–hexane, R_f 0.6). Its IR and NMR spectra were in accord with those reported in the literature.[17]

Reaction of 38 with Fe$_2$(CO)$_9$ in DMF. A mixture of 38 (833 mg, 3.06 mmol) and Fe$_2$(CO)$_9$ (1.31 g, 3.60 mmol) in DMF (10.5 mL) was stirred at 25 °C for 18 h under N$_2$. Octane was added to the reaction mixture as internal standard. GLC analysis (column E, 90 °C) indicated that 41 and 2,4-dimethylpentan-3-one were formed in 80 and 9% yields, respectively.

Reaction of 2,4-Dibromo-2-methylpentan-3-one (42) with Fe$_2$(CO)$_9$ in Methanol. A mixture of 42 (774 mg, 3.00 mmol) and Fe$_2$(CO)$_9$ (1.31 g, 3.60 mmol) in dry, degassed methanol (6.0 mL) was stirred at 25 °C for 38 h under argon. The mixture was quenched by the addition of saturated NaHCO$_3$ solution (10 mL) and extracted with CH$_2$Cl$_2$ (10 mL × 3). GLC analysis (column E, 50 °C) of the extract showed the absence of 2,4-dimethylpent-1-en-3-one (48). The combined organic extracts were dried over Na$_2$SO$_4$. The solvent was removed by distillation through a 30-cm Vigreux column under ordinary pressure, leaving a yellow oil (500 mg). To the residue was added a small amount of CH$_2$Cl$_2$ and the precipitated insoluble materials were filtered off. The filtrate was distilled with a bulb-to-bulb system, affording a 90:10 mixture (determined by NMR analysis) of 2-methoxy-2-methylpentan-3-one (44) and 2-methoxy-4-methylpentan-3-one (45) (bp 70–80 °C (bath temperature), 100 mm, 177 mg, 45% combined yield). The spectral properties (IR, NMR, and mass spectra) and chromatographic (GLC and TLC) behavior were quite identical with those of authentic samples prepared by the reported procedures.[41,53]

Reaction of 42 with Fe$_2$(CO)$_9$ in the Presence of Sodium Acetate in DMF. A mixture of 42 (258 mg, 1.00 mmol), Fe$_2$(CO)$_9$ (437 mg, 1.20 mmol), and anhydrous sodium acetate (410 mg, 5.00 mmol) in DMF (2.0 mL) was stirred at 25 °C for 16 h under argon. To this was added saturated Na$_2$edta solution (10 mL) and the mixture was extracted with 1:1 ethyl acetate–hexane (10 mL × 3). The combined extracts were dried over Na$_2$SO$_4$. GLC analysis (column E, 50 °C, methyl isopropyl ketone as internal standard) of the organic layer indicated the occurrence of a small amount (<3%) of 48 (t_R 6.3 min) and 2-methylpentan-3-one in 9% yield. Concentration of the organic extract under reduced pressure gave an oily residue (276 mg), which was distilled with a bulb-to-bulb apparatus to give a mixture of 2-acetoxy-2-methylpentan-3-one (46) and 2-acetoxy-4-methylpentan-3-one (47) contaminated with some DMF. The distillate was chromatographed (1:20 ethyl acetate–benzene), giving a 69:31 mixture of 46 and 47 (72 mg, 46% combined yield, R_f 0.4). IR of the mixture: 1737 (CH$_3$COO), 1727 cm^{-1} (C═O). Mass spectrum of the mixture: m/e 158 (M$^+$). NMR of 46: δ 1.03 (t, J = 7.0 Hz, CH$_2$C*H$_3$*), 1.43 (s, C(CH$_3$)$_2$), 2.06 (s, COCH$_3$), 2.40 (q, J = 7.0 Hz, C*H$_2$*CH$_3$). NMR of 47: δ 1.08 and 1.25 (two d, J = 7.0 Hz, CH(C*H$_3$*)$_2$), 2.11 (s, COCH$_3$), 2.81 (seven-line m, J = 7.0 Hz, C*H*(CH$_3$)$_2$), 5.16 (q, J = 7.0 Hz, C*H*OCOCH$_3$). The spectral data were identical with those of authentic samples prepared by the reported methods[54,55] followed by acetylation.

Reaction of 27 with Zn/Cu Couple in Benzene. A mixture of 27 (1.00 g, 2.70 mmol) and Zn/Cu couple (10.0 g, 153 mg-atom) in

benzene (40 mL) was heated at reflux with stirring for 48 h under N$_2$. The reaction mixture was passed through a Celite 545 pad and the filtrate was washed with 3 N HCl. The organic layer was dried over MgSO$_4$ and concentrated, leaving an oily material. The residue was distilled under reduced pressure (31 mm) and the fraction (550 mg) boiling at 135–140 °C was collected. GLC analysis (column C, 180 °C, methyl hexanoate as an internal standard) of the distillate showed the formation of 28 (11% yield), 30 (28% yield), 1-*tert*-butyl-5,7,7-trimethylbicyclo[3.1.1]heptan-6-one (49) (t_R 14.4 min, 40% yield), 2,6-di-*tert*-butyl-2-hydroxycyclohexanone (50) (t_R 28 min, 3% yield), and 51 (t_R 6.0 min, 4% yield). Analytical samples of 49 and 50 were obtained by preparative GLC (column B, 180 °C). 49: IR (neat film) 1770 cm^{-1} (C═O); NMR δ 0.80 (s, one of C(CH$_3$)$_2$), 1.03 (s, C(CH$_3$)$_3$), 1.18 (s, one of C(CH$_3$)$_2$ and CCH$_3$), 1.40–2.50 (m, 3 CH$_2$); mass spectrum m/e 208 (M$^+$). Anal. (C$_{14}$H$_{24}$O) C, H. 50: mp 74–75 °C; IR (KBr) 1710 cm^{-1} (C═O); NMR δ 0.95 (s, CHC(C*H$_3$*)$_3$), 1.02 (s, C(OH)C(C*H$_3$*)$_3$), 1.50–2.40 (m, CH and 3 CH$_2$), 2.98 (br s, OH); exact mass spectrum m/e 226.1941 (calcd for C$_{14}$H$_{26}$O$_2$, 226.1933).

Reaction of 27 with Ni(CO)$_4$ in Benzene. To a solution of 27 (2.50 g, 6.80 mmol) in benzene (40 mL) was added dropwise a solution of Ni(CO)$_4$ (1.30 mL, 1.77 g, 10.3 mmol) in the same solvent (10 mL) over a period of 15 min. The resulting mixture was stirred at 50 °C for 24 h under N$_2$. After concentration under reduced pressure, the insoluble precipitates were removed by filtration, and the filtrate was distilled (0.1 mm). The distillate (70 mg) collected at 70–80 °C (bath temperature) was subjected to GLC (column C, 180 °C), indicating the formation of 28 (5% yield) and 30 (64% yield).

References and Notes

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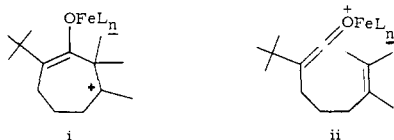
Reactions of Polybromo Ketones with 1,3-Dienes in the Presence of Iron Carbonyls. New 3 + 4 → 7 Cyclocoupling Reaction Forming 4-Cycloheptenones[1,2]

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Abstract: Oxyallyl species generated from α,α'-dibromo ketones and iron carbonyls cycloadd to both open-chain and cyclic 1,3-dienes in a 3 + 4 → 7 manner, giving 4-cycloheptenones in fair to good yields. Cyclopentadiene and furan serve as highly efficient receptors of the oxyallyl intermediates to give bicyclic cycloadducts. Pyrrole derivatives having an electron-withdrawing group at the nitrogen atom give the 3 + 4 cyclocoupling products, while *N*-methylpyrrole or thiophene produces the electrophilic substitution products. Although reaction of 1,3-dienes and α,α'-dibromoacetone, unlike other ordinary dibromo ketones, has failed to afford any cycloheptenone adduct, the cyclocoupling with α,α,α',α'-tetrabromoacetone proceeds smoothly. Thus iron carbonyl promoted reaction of tetrabromoacetone and 1,3-dienes followed by zinc–copper couple reduction formally corresponds to a 3 + 4 → 7 cyclocoupling of dibromoacetone and dienes.

The *cyclocoupling reactions*, defined broadly as ring formations by combining termini of two (or more) linear components irrespective of the detailed reaction mechanism, have occupied a most important position in the synthesis of organic structures.[3-10] The carbocyclic ring formations are formally classified according to the number of carbon units which participate in the coupling reaction as shown in eq 1–7. Reaction patterns of eq 1–3, forming even-numbered homocyclic systems, have various examples. Construction of cyclobutane rings, for instance, can be easily attained by [2 + 2] photocy-