(K.E.W.) gratefully acknowledges receipt of a University of Illinois Fellowship (1976–1977).

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Synthesis of 1,4-Diketones by Oxidative Coupling of Ketone Enolates with CuCl$_2$

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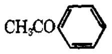
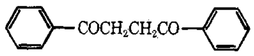
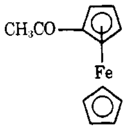
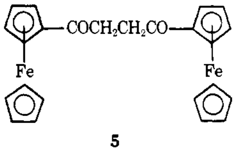
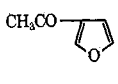
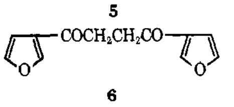
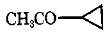
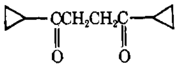
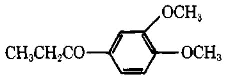
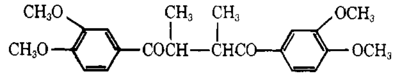
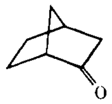
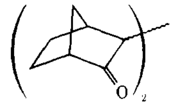
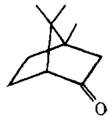
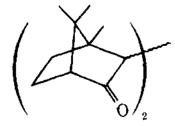
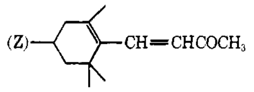
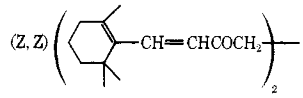
Abstract: A full scope of oxidative coupling of lithium enolates providing a general and efficient preparation of 1,4-diketones was examined. The oxidative coupling of lithium enolates was performed by treating ketone enolates, which were prepared from ketone and lithium diisopropylamide in THF at −78 °C, with CuCl$_2$ in DMF. The use of DMF cosolvent was very crucial in the copper promoted oxidative coupling of lithium enolates. Methyl ketones (RCOCH$_3$) were oxidatively dimerized to 1,4-diketones (RCOCH$_2$CH$_2$COR) in excellent to moderate yields; but, increasing alkyl substitution at the coupling site resulted in a remarkable reduction in the yield of 1,4-diketone. Cross coupling of two different methyl ketones (CH$_3$COR and CH$_3$COR′), in which a threefold excess of one ketone enolate over another is used, led to the formation of a specific unsymmetrical 1,4-diketone (RCOCH$_2$CH$_2$COR′) in a satisfactory yield and selectivity. *cis*-Jasmone (**22**) and allyl rethrone (**23**) were synthesized by a new route via the oxidative cross coupling of acetone with (*Z*)-5-octen-2-one and of acetone with 5-hexen-2-one, respectively. Intramolecular coupling of diketone dienolates was also examined. Diketone dienolate of 1,1′-diacetylferrocene was oxidatively cyclized to give α,α'-dioxotetramethyleneferrocene (**24**) in 55% yield, while diketone dienolate of 1,2-dipivaroylethane underwent dehydrogenation to give (*E*)-1,2-dipivaroylethylene (**27**) in 75% yield. Finally, the oxidative coupling of some vinylogs of methyl ketones and acetates such as (*E*)-2,2-dimethyl-4-hexen-3-one (**29**) and (*E*)-ethyl crotonate (**32**) was investigated. Lithium enolates of vinylogs of methyl ketones and acetates were generated in situ at −78 °C by treating vinylogs of methyl ketones and acetates with lithium diisopropylamide in a mixed solvent of THF and HMPA. It is noteworthy that the oxidative coupling of enolates of vinylogs of methyl ketones and acetates produced γ,γ-coupling dimers and α,γ-coupling dimers prominently. α,α-Coupling dimer was produced only in a trace amount. This finding is in remarkable contrast with the fact that the enolates of vinylogs of methyl ketones and acetates undergo the nucleophilic reaction (alkylation and protolysis) at the α carbon exclusively.

A variety of synthetic methods for the preparation of 1,4-diketones have been developed, since 1,4-diketones are versatile intermediates for syntheses of some natural products and related compounds consisting of cyclopentenone[1] and furan[2] ring systems. One of the representative and attractive routes to 1,4-diketones involves the conjugate addition of acyl anion equivalents, such as nitro-stabilized carbanion,[3] lithium di[bis(phenylthio)methyl]copper,[4] and acyl carbonylnickelate,[5] to enones. Many other synthetic routes to 1,4-diketones have been reported.[6]

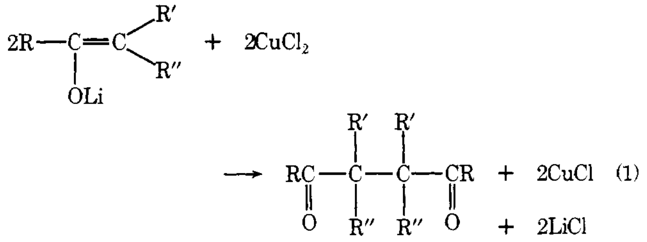
Transition metal promoted dimerization of carbanions has constituted a convenient method for the carbon–carbon bond formation in organic synthesis. Copper-promoted dimerizations of carbanions, which are stabilized by sulfonyl,[7] phos-

Table I. Synthesis of 1,4-Diketones by Oxidative Coupling of Ketone Enolates

No.	Starting ketones	1,4-Diketones (%)	
1		 **1**	(95)[a]
2	CH_3CH_2COPh	$PhCOCH(CH_3)CH(CH_3)COPh$ **2**	(28)[b,c]
3	$(CH_3)_2CHCOPh$	$PhCOC(CH_3)_2C(CH_3)_2COPh$ **3**	(2)[c]
4	$CH_3COC(CH_3)_2CO_2C_2H_5$	$H_5C_2O_2CC(CH_3)_2COCH_2CH_2COC(CH_3)_2CO_2C_2H_5$ **4**	(64)
5		 **5**	(78)
6		 **6**	(41)
7		 **7**	(46)
8		 **8**	(31)
9		 **9**	(73)[d]
10		 **10**	(60)[d]
11	$CH_3COCH_2CH_2CH{=}CH_2$	$CH_2{=}CHCH_2CH_2COCH_2CH_2COCH_2CH_2CH{=}CH_2$ **11** $CH_2{=}CHCH_2CH_2COCH_2CH(COCH_3)CH_2CH{=}CH_2$ **12**	(65) (7)
12		 **13**	(82)

[a] Reference 16. [b] *dl*/meso mixture. [c] Reference 17. [d] Exo–exo, exo–endo, and endo–endo mixture.

phoryl,[7] imidoyl,[7] and alkoxycarbonyl[8] groups, have been hitherto known. Therefore, the most straightforward approach to 1,4-diketones seemed to be the oxidative dimerization of ketone enolates (eq 1). However, no successful dimerization



$$2R{-}C(OLi){=}CR'R'' + 2CuCl_2 \longrightarrow RC({=}O){-}CR'R''{-}CR'R''{-}C({=}O)R + 2CuCl + 2LiCl \quad (1)$$

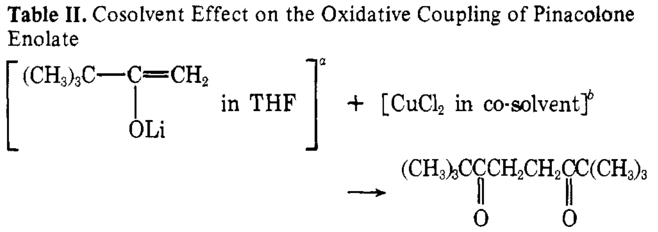
of ketone enolates by metal salts had been realized prior to our preliminary study,[9] which disclosed that 1,4-diketones were readily prepared by treating ketone enolates in THF at −78 °C with $CuCl_2$ in dimethylformamide (DMF). The use of DMF as a cosolvent was crucial in the oxidative dimerization of ketone enolates. This paper describes the full scope of the recently reported copper-promoted dimerization of lithium enolates, providing an efficient preparation of 1,4-diketones.[9]

Results and Discussion

As mentioned in a preliminary paper,[9] the $CuCl_2$-promoted dimerization of ketone enolates was simply performed in one flask by treating lithium enolate, which was generated in situ at −78 °C from ketone and lithium diisopropylamide in THF, with $CuCl_2$ in DMF. The dimerization of ketones bearing one kind of enolizable hydrogen gave a single 1,4-diketone according to eq 1. Methyl ketones ($RCOCH_3$) were dimerized to 1,4-diketones ($RCOCH_2CH_2COR$) in excellent to moderate yields; but, increasing alkyl substitution at the coupling site resulted in a remarkable reduction in the yield of 1,4-diketone (entry no. 1, 2, and 3 in Table I). This trend in the ketone dimerization was also observed in the 1,4-diketone synthesis by the oxidative coupling of silyl enol ether by Ag_2O,[10] probably due to steric hindrance in the transition state of ketone enolate dimerization.

The dimerization of ketones having two different enolizable

Table II. Cosolvent Effect on the Oxidative Coupling of Pinacolone Enolate

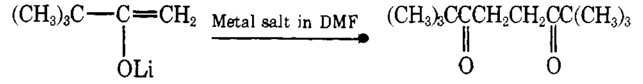


$$\left[(CH_3)_3C-\underset{OLi}{\underset{|}{C}}=CH_2 \text{ in THF}\right]^{a} + [CuCl_2 \text{ in co-solvent}]^{b} \longrightarrow (CH_3)_3C\underset{O}{\underset{\|}{C}}CH_2CH_2\underset{O}{\underset{\|}{C}}C(CH_3)_3$$

Cosolvent (ml)	Conditions of $CuCl_2$ in cosolvent	Product, %
DMF (7.5)	Brown solution	95
Me_2SO (15.0)	Pale-green suspension	12
HMPA (15.0)	Brown solution	10
THF (7.5)	Brown suspension	Tr
Toluene (7.5)	Brown suspension	0

[a] Lithium enolate of pinacolone was generated in site at −78 °C by adding dropwise pinacolone (4.5 mmol) to lithium diisopropylamide which was prepared from diisopropylamine (5.0 mmol) in dry THF (5 ml) and *n*-butyllithium (5.0 mmol, 15% hexane solution). [b] $CuCl_2$ (5 mmol) was mixed with cosolvent.

Table III. Dimerization of Lithium Enolate of Pinacolone in the Presence of Various Metal Salts

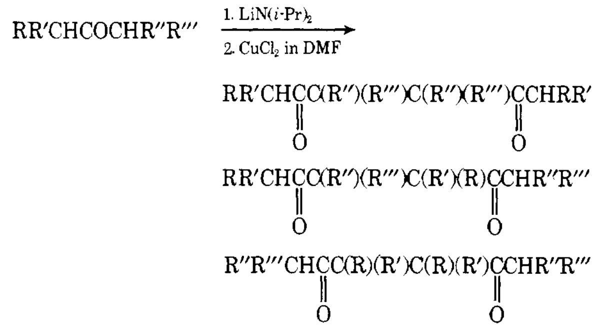


$$(CH_3)_3C-\underset{OLi}{\underset{|}{C}}=CH_2 \xrightarrow{\text{Metal salt in DMF}} (CH_3)_3C\underset{O}{\underset{\|}{C}}CH_2CH_2\underset{O}{\underset{\|}{C}}C(CH_3)_3$$

Metal salt (equiv)	Product, %
$CuCl_2$ (0.5)	25
$CuCl_2$ (1.0)	95
$CuCl_2$ (1.5)	86
$CuBr_2$ (1.0)	64
$Cu(acac)_2$ (1.0)	60
$Cu(OAc)_2$ (1.0)	24
$CuI-O_2$, $CuCl-O_2$ (1.0)[a]	0
AgCl, $AgNO_3$ (1.0)	Tr
$ZnCl_2$, $HgCl_2$, $CdCl_2$ (1.0)	0
$FeCl_3$, $CoCl_3$ (1.0)	Tr

[a] After lithium enolate was treated at −78 °C with Cu(I) salt in DMF, O_2 gas was continuously bubbled into the reaction mixture.

hydrogens could, in principle, give a mixture of three possible isomers of 1,4-diketones:



$$RR'CHCOCHR''R''' \xrightarrow[2.\ CuCl_2 \text{ in DMF}]{1.\ LiN(i\text{-}Pr)_2} \begin{array}{l} RR'CH\underset{O}{\underset{\|}{C}}C(R'')(R''')C(R'')(R''')\underset{O}{\underset{\|}{C}}CHRR' \\ RR'CH\underset{O}{\underset{\|}{C}}C(R'')(R''')C(R')(R)\underset{O}{\underset{\|}{C}}CHR''R''' \\ R''R'''CH\underset{O}{\underset{\|}{C}}C(R)(R')C(R)(R')\underset{O}{\underset{\|}{C}}CHR'R''' \end{array} \quad (2)$$

Actually, the least crowded 1,4-diketone was, as expected, produced predominantly together with the more crowded 1,4-diketone as a minor product, both of which were separated and isolated by preparative GLC or TLC (entry no. 11 in Table I). The most crowded 1,4-diketone was produced in a negligible amount under the reaction conditions employed. It has also been demonstrated in a preliminary paper[9] that the use of silyl enol ether instead of ketone as a starting material in the procedure for the oxidative coupling of ketone enolates allowed the regiospecific dimerization of unsymmetrical ketone having two different enolizable hydrogens. New data on the 1,4-diketone synthesis by the oxidative coupling of ketone enolates are listed in Table I. As seen in Table I, the technique for the ketone dimerization is applicable to a wide range of ketones. It is noteworthy that the presence of olefin, cyclopropyl, ferrocenyl groups, and ester function is tolerated.

As aforementioned, DMF plays a decisive role as a cosolvent in the present oxidative coupling of ketone enolates. Now, some solvents were examined in the dimerization of pinacolone enolate (Table II). The use of dimethyl sulfoxide (Me_2SO) and hexamethylphosphoric triamide (HMPA) as cosolvent is not practical because 1,4-diketone was produced only in low yields. The less polar solvents such as THF and toluene were ineffective. As to the role of DMF cosolvent in the oxidative coupling of ketone enolates, solvation of ketone enolate by DMF and solubility of $CuCl_2$ in DMF may be conceivable, but the detailed mechanism is the subject of future study.

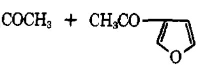
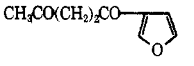
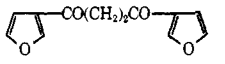
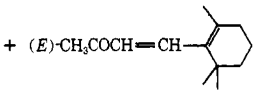
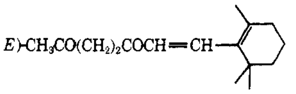
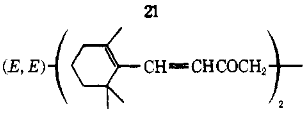
The effect of metal salts was also examined in the dimerization of pinacolone enolate (Table III). As evident in Table III, cupric salts, especially $CuCl_2$, were specific in the oxidative coupling of ketone enolates. It is noted that a combination of cuprous salt and oxygen, which sometimes functions like cupric salt in oxidative coupling of carbanions,[7a] had no effect in the present coupling reaction. The results with some varying amounts of $CuCl_2$ indicated that an equivalent of $CuCl_2$ is requisite to the effective coupling of lithium enolate, being in accord with the stoichiometry shown in eq 1.

Cross Coupling of Ketone Enolates. As expected, the cross coupling of two different ketones, each of which has two enolizable hydrogens, yielded a complex mixture of all possible 1,4-diketones including unsymmetrical 1,4-diketones as cross coupling products; but, it was found that, in the cross coupling reaction of two different methyl ketones (CH_3COR and CH_3COR'), the use of a large excess of one ketone enolate over another led to the formation of a specific unsymmetrical 1,4-diketone, $RCOCH_2CH_2COR'$, in a synthetically useful yield and selectivity. The approach to the preparation of unsymmetrical 1,4-diketones may be of preparative value, since unsymmetrical 1,4-diketones, $RCOCH_2CH_2COR'$, are important precursors to some natural products consisting of cyclopentenone and furan ring systems. Some cross couplings have been exemplified in a previous communication;[9] e.g., undecane-2,5-dione, a precursor of dihydrojasmone, was prepared in a satisfactory yield and selectivity by the cross coupling reaction of 3 mol of acetone enolate and 1 mol of 2-octanone enolate. The present paper describes some other syntheses of unsymmetrical 1,4-diketones, $CH_3COCH_2CH_2COCH_2R$, by the oxidative cross couplings of acetone and methyl ketones (CH_3COCH_2R), which involve natural products or their precursors. The cross coupling was carried out as follows. $CuCl_2$ (4.5 mmol) in DMF (7.5 ml) was added all at once to a 3:1 mixture of lithium enolates of acetone and methyl ketone at −78 °C, prepared by addition of a mixture of acetone (3 mmol) and methyl ketone (1 mmol) to lithium diisopropylamide (4.5 mmol) in THF (10 ml). A desired 1,4-diketone ($CH_3COCH_2CH_2COCH_2R$) was separated and isolated by gas chromatography or TLC from other 1,4-diketones:

$$3CH_3COCH_3 + 1CH_3COCH_2R \xrightarrow[2.\ 4.5 \text{ equiv } CuCl_2]{1.\ 4.5 \text{ equiv } LiN(i\text{-}Pr)_2} \left\{\begin{array}{l} CH_3COCH_2CH_2COCH_2R \\ CH_3COCH_2CH(R)COCH_3 \\ CH_3COCH_2CH_2COCH_3 \end{array}\right. \quad (3)$$

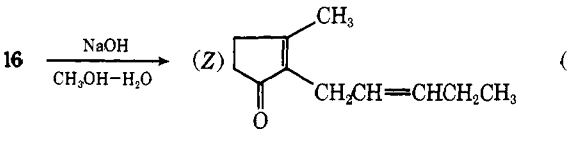
Results of the cross couplings are summarized in Table IV. (*Z*)-8-Undecene-2,5-dione (**16**) obtained by the cross coupling of acetone and (*Z*)-5-octen-2-one enolates was converted to *cis*-jasmone (**22**) by the conventional alkali treatment.[1,11] Similarly, allyl rethrone (**23**) was synthesized by intramolecular aldol condensation of 1-nonene-5,8-dione (**18**) obtained from the cross coupling of acetone and 5-hexen-2-one eno-

Table IV. Cross Coupling of Lithium Enolates of Acetone and Methyl Ketone

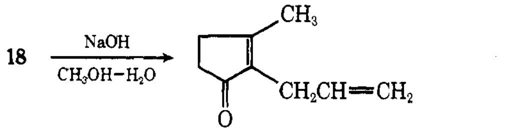
Ketones	Coupling products (%)	
CH_3COCH_3 + (Z)-$CH_3CO(CH_2)_2CH{=}CHC_2H_5$ **14**	(Z)-$CH_3CO(CH_2)_2CO(CH_2)_2CH{=}CHC_2H_5$ **16**	(68)
	(Z)-$CH_3COCH_2CH(COCH_3)CH_2CH{=}CHC_2H_5$ **17**	(1)
	$CH_3CO(CH_2)_2COCH_3$[a]	
CH_3COCH_3 + $CH_3CO(CH_2)_2CH{=}CH_2$ **15**	$CH_3CO(CH_2)_2CO(CH_2)_2CH{=}CH_2$ **18**	(53)
	$CH_3COCH_2CH(COCH_3)CH_2CH{=}CH_2$ **19**	(1)
	$CH_3CO(CH_2)_2COCH_3$[a]	
CH_3COCH_3 + 	 **20**	(59)
	 **6**	(4)
	$CH_3CO(CH_2)_2COCH_3$[a]	
CH_3COCH_3 + 	 **21**	(65)
	 **13**	(2)
	$CH_3CO(CH_2)_2COCH_3$[a]	

[a] Hexane-2,5-dione was produced in about 40–50% yield based upon acetone used.

lates.[1,11] The cross coupling of acetone and β-acetylfuran enolates presents a most convenient route to ipomeanine (**20**).


(4)

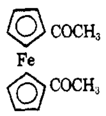
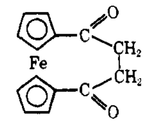
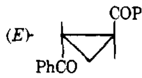
22


(5)

23

Intramolecular Coupling of Diketone Dienolates. As an extension of the oxidative coupling of ketone enolates we have examined intramolecular coupling of diketone dienolates which may give rise to the formation of cyclic 1,4-diketones. All attempts to prepare cyclic 1,4-diketones by intramolecular couplings of dienolates of $CH_3CO(CH_2)_nCOCH_3$ ($n = 2, 4, 6, 8, 12$) produced a complex mixture of polymeric 1,4-diketones. However, the intramolecular couplings of 1,1-diacetylferrocene and 1,3-dibenzoylpropane furnished the desired α,α′-dioxotetramethyleneferrocene (**24**) and (E)-dibenzoylcyclopropane (**25**) in 55 and 50% yields, respectively. The synthesis of **24** presents a most convenient method for conjunction of two cyclopentadiene rings of ferrocene by a C_4 chain. So far, the preparation of tetramethyleneferrocene derivatives has been accomplished via multisteps.[12] On the other hand, the $CuCl_2$ treatment of diketone dienolates derived from 1,2-dibenzoylethane and 1,2-dipivaroylethane yielded olefinic diketones, (E)-1,2-dibenzoylethylene (**26**) and (E)-1,2-dipivaroylethylene (**27**), respectively. Similarly, diethyl succinate was also oxidized to give diethyl fumarate in 53% yield. Results are summarized in Table V. Despite serious limitations, the oxidative intramolecular coupling of diketone dienolates gives rapid access to some cyclic diketones and 1,2-diacyl olefins from readily available starting materials and it is also a "one-pot" procedure.

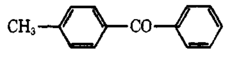
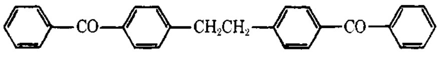
Table V. Intramolecular Coupling of Diketone Dienolates

No.	Diketone	Coupling product (%)	
1		 **24**	(55)
2	$PhCOCH_2CH_2CH_2COPh$	 **25**	(50)[a]
3	$PhCOCH_2CH_2COPh$	(E)-$PhCOCH{=}CHCOPh$ **26**	(52)[b]
4	$(CH_3)_3CCOCH_2CH_2COC(CH_3)_3$[c]	(E)-$(CH_3)_3CCOCH{=}CHCOC(CH_3)_3$ **27**	(75)[d]
5	$C_2H_5O_2CCH_2CH_2CO_2C_2H_5$	(E)-$C_2H_5O_2CCH{=}CHCO_2C_2H_5$ **28**	(53)

[a] Reference 18. [b] Reference 19. [c] Reference 9. [d] Reference 20.

Oxidative Coupling of Vinylogs of Carbonyl Compounds. Lithium enolates generated from α,β-unsaturated carbonyl compounds are potentially ambident in their behavior toward carbon alkylation.[13] Conceptually, an alkylating agent may react at the α and γ carbons of an α,β-unsaturated carbonyl compound. Practically, alkylation of lithium enolates of α,β-unsaturated carbonyl compounds occurs selectively at the α carbon. Herein, the oxidative dimerizations of some vinylogs of methyl ketones and acetates such as (E)-2,2-dimethyl-4-hexen-3-one (**29**) and ethyl (E)-crotonate (**32**) have been examined. Lithium enolate of **29** was prepared in situ by treating

Table VI. Oxidative Coupling of Vinylogs of Carbonyl Compounds

No.	Vinylogs of carbonyl compounds	Dimeric products (%)	
1	(*E*)-$CH_3CH{=}CHCOC(CH_3)_3$ **29**	(*E,E*)-$(CH_3)_3CCOCH{=}CHCH_2CH_2CH{=}CHCOC(CH_3)_3$ **34**	(33)
		(*E*)-$(CH_3)_3CCOCH{=}CHCH_2CH(CH{=}CH_2)COC(CH_3)_3$ **35**	(32)
2	(*E*)-$CH_3CH{=}C(CH_3)_3COC(CH_3)_3$ **30**	(*E,E*)-$(CH_3)_3CCOC(CH_3){=}CHCH_2CH_2CH{=}C(CH_3)COC(CH_3)_3$ **36**	(55)
		(*E*)-$(CH_3)_3CCOC(CH_3){=}CHCH_2C(CH_3)(CH{=}CH_2)COC(CH_3)_3$ **37**	(20)
3	 **31**	 **38**	(48)[a]
4	(*E*)-$CH_3CH{=}CHCO_2C_2H_5$ **32**	(*E,E*)-$C_2H_5O_2CCH{=}CHCH_2CH_2CH{=}CHCO_2C_2H_5$ **39**	(27)
		(*E*)-$C_2H_5O_2CCH{=}CHCH_2CH(CH{=}CH_2)CO_2C_2H_5$ **40**	(40)
5	(*E*)-$CH_3CH{=}C(CH_3)CO_2C_2H_5$ **33**	(*E,E*)-$C_2H_5O_2CC(CH_3){=}CHCH_2CH_2CH{=}C(CH_3)CO_2C_2H_5$ **41**	(33)
		(*E*)-$C_2H_5O_2CC(CH_3){=}CHCH_2C(CH_3)(CH{=}CH_2)CO_2C_2H_5$ **42**	(20)

[a] Reference 21.

diisopropylamine in THF–HMPA (4:1) with *n*-butyllithium at −78 °C, followed by addition of **29**. Treatment of the lithium enolate of **29** with $CuCl_2$ in DMF afforded a mixture of isomeric coupling dimers of **29**. The reaction mixture was worked up (see Experimental Section) without heat treatment and chromatographed on silica gel (chloroform–hexane (1:2)) to give γ,γ-coupling dimer (**34**) and α,γ-coupling dimer (**35**) in 33 and 32% yield, respectively. α,α-Coupling dimer was produced only in a negligible yield, if any. The findings indicate that γ,γ-coupling dimer was initially produced, but not derived via thermal rearrangement of α,α-coupling dimer. Similar results were obtained in the oxidative couplings of some α,β-unsaturated ketones and esters (Table VI). It is noteworthy that the coupling of enolates of α,β-unsaturated carbonyl compounds took place at the γ carbon more prominently than at the α carbon. Substitution on the α carbons of α,β-unsaturatd carbonyl compounds led to an increase in the ratio of γ,γ-coupling dimer to α,γ-coupling dimer. This observation may be taken to indicate that steric factors are controlling the $CuCl_2$-promoted dimerization of ketone enolates. It is in remarkable contrast with the fact that the enolates of α,β-unsaturated carbonyl compounds undergo nucleophilic reaction (alkylation and protolysis) exclusively at the carbon α to the carbonyl group.[14] Our results may be pertinent to the recent Katzenellenbogen's findings that copper salts of dianions of α,β-unsaturated acids undergo selective γ alkylation.[15]

$$CH_3CH{=}CHCOR \xrightarrow[2.\ CuCl_2]{1.\ LiN(i\text{-}Pr)_2} \left\{ \begin{array}{l} RCOCH{=}CHCH_2CH_2CH{=}CHCHCOR \\ \quad (\gamma,\gamma\text{-coupling dimer}) \\ RCOCH{=}CHCH_2CH(CH{=}CH_2)COR \\ \quad (\alpha,\gamma\text{-coupling dimer}) \\ RCOCH(CH{=}CH_2)CH(CH{=}CH_2)COR \\ \quad (\alpha,\alpha\text{-coupling dimer}) \end{array} \right. \quad (6)$$

Experimental Section

Materials. Ethyl α,α-dimethyl acetoacetate,[22] β-acetylfuran,[23] cyclopropyl methyl ketone,[24] 3′,4′-dimethoxypropiophenone,[25] and 2-norbornanone[26] were prepared by previously reported procedures, respectively. (*Z*)-5-Octen-2-one (**13**)[27] was prepared from 2-lithio-2-methyl-1,3-dithiane[28] and (*Z*)-1-bromo-3-hexene.[29] (*E*)-2,2-Dimethyl-4-hexen-3-one (**26**) [IR (neat) 1680, 1660 cm^{-1}; NMR (CCl_4) δ 1.10 (s, 9 H), 1.85 (dd, 3 H), 6.33 (d, *J* = 16.5 Hz, 1 H), 6.60 ∼ 7.05 (dq, 1 H)] was prepared by aldol condensation of pinacolone with acetaldehyde[30] and subsequent dehydration (1 h reflux in benzene with *p*-toluenesulfonic acid). (*E*)-2,2,4-Trimethyl-4-hexen-2-one (**27**) [IR (neat) 1680, 1660 cm^{-1}; NMR (CCl_4) δ 1.19 (s, 9 H), 1.50 ∼ 1.90 (m, 6 H), 5.70 ∼ 6.20 (m, 1 H)] was prepared by aldol condensation of 2,2-dimethyl-3-pentanone with acetaldehyde and subsequent dehydration. Other starting ketones and esters which are commercially available were distilled under nitrogen prior to use.

THF, DMF, HMPA, and diisopropylamine were dried over lithium aluminum hydride, calcium hydride, calcium hydride, and sodium metal, respectively, and distilled under nitrogen prior to use.

Anhydrous $CuCl_2$ was obtained by drying $CuCl_2{\cdot}2H_2O$ at 100 °C in oven. Other metal salts were dried in vacuo in a desiccator containing blue silica gel.

Oxidative Dimerization of Ethyl α,α-Dimethylacetoacetate. Under nitrogen, a solution of diisopropylamine (5 mmol) in dry THF (5 ml) was treated with *n*-butyllithium (5 mmol, 15% hexane solution) at −78 °C, and after 15 min, 0.72 g (4.5 mmol) of ethyl α,α-dimethylacetoacetate was added to the resulting THF solution of lithium diisopropylamide (LDA). After 15 min, anhydrous $CuCl_2$ (5 mmol) dissolved in 7.5 ml of DMF was added at once to the THF solution of lithium enolate of ethyl α,α-dimethylacetoacetate at the same temperature. The dark-green solution was stirred for an additional 30 min and then allowed to reach room temperature. The reaction mixture became dark brown and homogeneous. The reaction mixture was treated with 3% aqueous HCl and extracted with ether. The ether extract was washed twice with 3% aqueous HCl and then with water and dried over $MgSO_4$. The ether solution was evaporated and chromatographed on silica gel (chloroform eluent) to give 455 mg (64%) of 2,7-dicarbethoxy-2,7-dimethyloctane-3,6-dione (**4**); TLC R_f 0.6, chloroform. **4**: IR (neat) 1745, 1715 cm^{-1}; NMR (CCl_4 with Me_4Si) δ 1.27 (t, 6 H), 1.31 (s, 6 H), 2.66 (s, 4 H), 4.16 (q, 4 H). Anal. ($C_{16}H_{26}O_6$) C, H.

Oxidative Dimerization of Acetylferrocene. To a THF solution of LDA (5 mmol) at −78 °C prepared according to the procedure mentioned above, 1.02 g (4.5 mmol) of acetylferrocene in THF (3 ml) was added with stirring under nitrogen. After 15 min, anhydrous $CuCl_2$ (5 mmol) dissolved in 7.5 ml of DMF was added all at once at the same temperature. The reaction mixture was stirred for an additional 30 min and then allowed to reach room temperature. The reaction mixture was treated with 3% aqueous HCl and extracted with chloroform. The chloroform extract was washed with 3% aqueous HCl and with water and dried over $MgSO_4$. After removal of the solvent, the residue was dissolved in benzene and chromatographed on silica gel (chloroform eluent) to afford 788 mg (78%) of 1,2-diferrocenoylethane (**5**) in the form of orange needles, mp 184 ∼ 185 °C (lit.[31] 185 ∼ 186 °C); TLC R_f 0.5, chloroform. The structure of **5** was confirmed by comparing the spectral data with those of the authentic sample.

Oxidative Dimerization of β-Acetylfuran. According to the procedure mentioned above, lithium enolate of β-acetylfuran (0.88 g, 8 mmol) was treated with anhydrous $CuCl_2$ (9 mmol) in DMF (15 ml) at −78 °C. The reaction mixture was worked up with acid and extracted with ether. Product of 1,2-di(2-furoyl)ethane (**6**) (mp 158 ∼ 159 °C) (360 mg, 41% yield) was isolated by column chromatography on silica gel ($CHCl_3$ eluent); TLC R_f 0.4, chloroform. **6:** IR (KBr) 1655 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 3.17 (s, 4 H), 6.76 (m, 2 H), 7.42 (m, 2 H), 8.10 (m, 2 H). Anal. ($C_{12}H_{10}O_4$) C, H.

Oxidative Dimerization of Cyclopropyl Methyl Ketone. A THF solution of lithium enolate of cyclopropyl methyl ketone (0.38 g, 4.5 mmol) was reacted with $CuCl_2$ (5 mmol) in DMF (7.5 ml) at −78 °C. Product of 1,4-dicyclopropylbutan-1,4-dione (**7**) was isolated in 46% yield (175 mg) by preparative GLC (1.5 m × 3 mm, 10% Silicone DC 550 on Shimalite W at 180 °C, H_2 carrier gas 1.0 kg/cm^2, retention time of 4.2 min). **7:** IR (neat) 3080, 1700, 1020 cm^{-1}; NMR (CCl_4 with Me_4Si) δ 0.51 ∼ 1.18 (m, 8 H), 1.66 ∼ 2.15 (m, 2 H), 2.61 (s, 4 H). Anal. ($C_{10}H_{14}O_2$) C, H.

Oxidative Dimerization of 3′,4′-Dimethoxypropiophenone. A THF solution of lithium enolate of 3′,4′-dimethoxypropiophenone (1.56 g, 8 mmol) was reacted with $CuCl_2$ (9 mmol) in DMF (15 ml). Product of 1,4-diketone **8** (mp 177 ∼ 178 °C) was isolated in 31% yield (483 mg) by preparative TLC (silica gel, 1:1 chloroform–benzene); TLC R_f 0.3, 1:1 chloroform–benzene. **8:** IR (KBr) 1660 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 1.25 and 1.09 (two d, 6 H), 2.50 ∼ 3.50 (m, 2 H), 3.90 and 3.94 (2 s, 12 H), 6.65 ∼ 6.95 (m, 2 H), 7.35 ∼ 7.75 (m, 4 H). Anal. ($C_{22}H_{26}O_6$) C, H.

Oxidative Dimerization of 2-Norboranone. A THF solution of lithium enolate of 2-norbornanone (0.50 g, 4.5 mmol) was reacted with $CuCl_2$ (5 mmol) in DMF (7.5 ml) at −78 °C. Product of 1,4-ketone (**9**) was obtained as crystalline solid in 73% yield (365 mg) by preparative TLC (silica gel, chloroform); TLC R_f 0.5, chloroform. GLC analysis showed that 1,4-diketone **9** is a mixture of three isomers (55:40:5). **9:** IR (KBr) 1732 cm^{-1}; mass $M^+ = 218$. Anal. ($C_{14}H_{18}O_2$) C, H.

By the similar procedure, oxidative dimerization of camphor afforded 1,4-diketone (**10**) in 60% yield; TLC on silica gel, R_f 0.5, chloroform. **10:** IR (KBr) 1730 cm^{-1}; mass $M^+ = 300$. Anal. ($C_{20}H_{30}O_2$) C, H.

Oxidative Dimerization of 5-Hexen-2-one. A THF solution of lithium enolate of 5-hexen-2-one (0.45 g, 4.5 mmol) was reacted with $CuCl_2$ (5 mmol) in DMF (7.5 ml) at −78 °C. Two isomeric 1,4-diketones **11** and **12** were separated and isolated in 65% (290 mg) and 7% (31 mg) yields, respectively, by preparative GLC (1.5 m × 0.3 mm, 10% PEG 20M on Shimalite at 200 °C, H_2 carrier gas 1 kg/cm^2; **11:** retention time of 8.4 min; **12:** retention time of 4.9 min). **11:** IR (neat) 3050, 1710, 1640 cm^{-1}; NMR (CCL_4 with Me_4Si) δ 2.00 ∼ 2.70 (m, 8 H), 2.61 (s, 4 H), 4.80 ∼ 4.90 (m, 2 H), 4.90 ∼ 5.20 (m, 2 H), 5.40 ∼ 6.10 (m, 2 H). Anal. ($C_{12}H_{18}O_2$) C, H. **12:** IR (neat) 3050, 1710, 1640 cm^{-1}; NMR (CCl_4 with Me_4Si) δ 2.30 (s, 3 H), 2.10 ∼ 3.10 (m, 9 H) 4.80 ∼ 5.30 (m, 4 H) 5.50 ∼ 6.10 (m, 2 H). Anal. ($C_{12}H_{18}O_2$) C, H.

Oxidative Dimerization of β-Ionone. A THF solution of lithium enolate of β-ionone (0.86 g, 4.5 mmol) was reacted with $CuCl_2$ (5 mmol) in DMF (7.5 ml) at −78 °C. Product of 1,4-ketone (**13**) was isolated in 82% yield (704 mg) by column chromatography on aluminum oxide (hexane); TLC R_f 0.5, hexane. **13:** IR (neat) 1670, 1605 cm^{-1}; NMR (CCl_4 with Me_4Si) δ 1.02 (s, 12 H), 1.35 ∼ 1.70 (m, 8 H), 1.75 (s, 6 H), 1.90 ∼ 2.20 (m, 4 H), 2.80 (s, 4 H), 6.10 (d, $J = 16.5$ Hz, 2 H), 7.28 (d, $J = 16.5$ Hz, 2 H), Anal. ($C_{26}H_{38}O_2$) C, H.

Oxidative Cross Coupling of Acetone and (*Z*)-5-Octen-2-one (14). Under nitrogen, a solution of diisopropylamine (9 mmol) in dry THF (10 ml) was treated with *n*-butyllithium (9 mmol, 15% hexane solution) at −78 °C, and after 15 min, a mixture of 0.26 g (2 mmol) of (*Z*)-5-octen-2-one and 0.35 g (6 mmol) of acetone was added dropwise. After 15 min, $CuCl_2$ (9 mmol) in 15 ml of DMF was added to the mixture of lithium enolates of acetone and **14** at the same temperature. The resulting green solution was stirred for an additional 30 min and then allowed to reach room temperature. The reaction mixture was treated with 3% aqueous HCl and extracted with ether. The ether solution was washed with 3% aqueous HCl and with water and dried over $MgSO_4$. After removal of ether solvent, the residue was distilled in vacuo to afford 247 mg of (*Z*)-8-undecene-2,5-dione (**16,** 68% based on **14** used) and (*Z*)-4-acetyl-6-nonen-2-one (**17,** 1% based on **14** used) along with hexane-2,5-dione. Product **16** was separated and isolated by preparative GLC (1.5 m × 0.3 mm, 10% Silicone DC 550 on Shimalite W at 200 °C, H_2 carrier gas 1 kg/cm^2, retention time of 5.2 min). **16** was identified by comparison of its spectral data with those of authentic sample.[1]

By a similar procedure, oxidative cross couplings of acetone–5-hexen-2-one, acetone–β-acetylfuran, and acetone–β-ionone took place. Products of 8-nonene-2,5-dione (**18,** 53% based upon 5-hexen-2-one used) and 4-acetyl-6-hepten-2-one (**19,** 1% based upon 5-hexen-2-one used) were obtained along with hexane-2,5-dione. **18** was separated and isolated by preparative GLC, (1.5 m × 0.3 mm, 10% Silicone DC 550 on Shimalite W at 200 °C, H_2 carrier gas 1 kg/cm^2, retention time of 4.5 min) and identified by comparison of its spectral data with those of the authentic sample.[1] Products of β-(γ-oxovaleroyl)furan (**20**) (mp 41 ∼ 42 °C) and 1,2-(2-furoyl)ethane (**6**) were separated and isolated by column chromatography on silica gel ($CHCl_3$) in 59 and 4% yields, respectively; TLC of **20,** R_f 0.4, chloroform. **20:** IR (neat) 3125, 1720, 1680 cm^{-1}; NMR (CCl_4 with Me_4Si) δ 2.12 (s, 3 H), 2.74 (d, 2 H), 2.85 (d, 2 H), 6.60 ∼ 6.70 (m, 1 H), 7.90 ∼ 8.10 (m, 1 H), 8.30 ∼ 8.40 (m, 1 H). Anal. ($C_9H_{10}O_3$) C, H.

Products of the cross dimer (**21**) was separated and isolated by column chromatography on aluminum oxide (hexane) in 65% yield; TLC of **21,** R_f 0.4, hexane. **21:** IR (neat) 1700 ∼ 1670, 1600 cm^{-1}; NMR (CCl_4 with Me_4Si) δ 1.03 (s, 6 H), 1.40 ∼ 1.60 (m, 4 H), 1.75 (s, 3 H), 1.90 ∼ 2.20 (m, 2 H), 2.13 (s, 3 H), 2.65 (s, 4 H), 6.06 (d, $J = 16.5$ Hz, 1 H), 7.22 (d, $J = 16.5$ Hz, 1 H). Anal. ($C_{16}H_{24}O_2$) C, H.

Synthesis of *cis*-Jasmone (22). A mixture of 277 mg (1.50 mmol) of (*Z*)-8-undecene-2,5-dione (**16**) and 3 ml of 10% NaOH solution in methanol–water (1:1) was heated at 40 °C for 4 h. The reaction mixture was extracted with ether to afford 215 mg (87%) of jasmone (**22**). *cis*-Jasmone (**22**) was identified by comparison of its IR spectrum with that of an authentic sample.[32]

In a similar way, allyl rethrone (**23**) was synthesized in 80% yield by treatment of **18** with NaOH. Allyl rethrone (**23**) was identified by comparison of its IR spectrum with that of the authentic sample.[32]

Oxidative Intramolecular Coupling of 1,1′-Diacetylferrocene. Under a nitrogen atmosphere, a solution of diisopropylamine (10 mmol) in 20 ml of dry THF was treated with *n*-butyllithium (10 mmol) at −78 °C, and after 15 min, 1.21 g (4.5 mmol) of 1,1′-diacetylferrocene in 10 ml of THF was added dropwise with stirring. After 15 min, $CuCl_2$ (10 mmol) in DMF (15 ml) was added at once at the same temperature. The reaction mixture was stirred for an additional 30 min and then allowed to reach room temperature. The reaction mixture was treated with 3% aqueous HCl and extracted with chloroform. The chloroform solution was washed with 3% aqueous HCl and with water and dried over $MgSO_4$. After removal of chloroform, the residue was purified by column chromatography (silica gel). Elution with chloroform afforded 655 mg (55%) of 1,1′-(α,α′-dioxotetramethylene) ferrocene (**24**) [ruby red crystalline, mp 185 ∼ 186 °C, sublime at 135 °C (0.2 mmHg)]; TLC R_f 0.3, chloroform. **24:** IR (KBr) 3075 1660, 1650 cm^{-1}; NMR ($CDCl_3$) δ 2.96 (s, 4 H), 5.55 (m, 4 H), 5.82 (m, 4 H). Anal. ($C_{14}H_{12}O_2Fe$) C, H.

Oxidative intramolecular coupling of 1,3-dibenzoylpropane was performed according to the procedure mentioned above. The product of (*E*)-1,2-dibenzoylcyclopropane (**25**) was identified by comparison of its spectral data with those of an authentic sample.[18]

Oxidative Dehydrogenation of 2,2,7,7-Tetramethyloctane-3,6-dione. Under nitrogen, 0.90 g (4.5 mmol) of 2,2,7,7-tetramethyloctane-3,6-dione was added to LDA (10 mmol) in 20 ml of THF at −78 °C. After 15 min, $CuCl_2$ (10 mmol) in 15 ml of DMF was added at once at the same temperature. The reaction mixture was stirred for an additional 30 min and then allowed to reach room temperature. Product of (*E*)-2,2,7,7-tetramethyl-4-octene-3,6-dione (**27**)[20] was isolated in 75% yield (671 mg) by preparative GLC (1.5 m × 0.3 mm, 10% Silicone DC 550 on Shimalite W at 200 °C, H_2 carrier gas 0.4 kg/cm^2, retention time of 2.9 min).

Oxidative dehydrogenations of 1,2-dibenzoylethane and diethyl succinate were carried out by a similar procedure.

Oxidative Dimerization of (*E*)-2-2-Dimethyl-4-hexen-3-one (29). Under a nitrogen atmosphere, a solution of diisopropylamine (5 mmol) in dry THF (8 ml) and hexamethylphosphoramide (HMPA) (2 ml) was treated with *n*-butyllithium (5 mmol, 15% hexane solution) at −78 °C. After 15 min, 0.57 g (4.5 mmol) of (*E*)-2,2-dimethyl-4-hexen-3-one (**29**) was added dropwise with stirring to this solution. After 15 min, anhydrous $CuCl_2$ (5 mmol) in DMF (7.5 ml) was added at once at the same temperature. The dark-green solution was stirred for an additional 30 min and then allowed to reach room temperature. The reaction mixture was worked up with acid, extracted with ether, and concentrated in vacuo at room temperature. Column chromatography on silica gel (chloroform–hexane (1:2)) of the residue gave two isomeric coupling products (**34**) and (**35**) in 33% (186 mg) and 32% (180 mg) yield: TLC, **34:** R_f 0.4, 1:2 chloroform–hexane, **35:** R_f 0.6, 1:2 chloroform–hexane; GLC (1.5 m × 3 mm, 10% PEG 20 M on Shimalite at 200 °C, H_2 carrier gas 1 kg/cm^2, **34:** retention time of 13.0 min, **35:** retention time of 5.2 min). **34:** IR (neat) 1685, 1630 cm^{-1}; NMR (CCl_4 with Me_4Si) δ 1.09 (s, 18 H), 2.2 $\sim$ 2.4 (m, 4 H), 6.0 $\sim$ 7.0 (m, 6 H). Anal. ($C_{16}H_{26}O_2$) C, H. **35:** IR (neat) 1695, 1685, 1630, 990, 910 cm^{-1}; NMR (CCl_4 with Me_4Si) δ 1.00 (two s, 18 H), 2.0 $\sim$ 2.5 (m, 2 H), 3.4 $\sim$ 3.9 (m, 1 H), 4.7 $\sim$ 5.7 (m, 3 H), 6.0 $\sim$ 6.8 (m, 2 H). Anal. ($C_{16}H_{26}O_2$) C, H. *E,E* stereochemistry of **34** and *E* stereochemistry of **35** were determined by comparison of their NMR signal patterns with those of (*E,E*)-1,6-dicarbethoxy-1,5-hexadiene (**39**) and (*E*)-1,4-dicarbethoxy-1,5-hexadiene (**40**), respectively, of which stereochemistry was established on the basis of the NMR coupling constants of the olefinic protons.

Oxidative dimerization of (*E*)-2,2,4-trimethyl-4-hexen-3-one (**30**) was carried out by a similar procedure. Products of **36** and **37** were separated and isolated by column chromatography on silica gel (hexane–chloroform (1:1)); TLC, **36:** R_f 0.5, 1:1 hexane–chloroform, **37:** R_f 0.7, 1:1 hexane-chloroform. **36:** IR (neat) 1680, 1660 cm^{-1}; NMR (CCl_4 with Me_4Si) δ 1.17 (s, 18 H), 1.75 (broad s, 6 H), 2.10 $\sim$ 2.40 (m, 4 H) 5.70 $\sim$ 6.30 (m, 2 H). Anal. ($C_{18}H_{30}O_2$) C, H. **37:** IR (neat) 1690, 1660, 1640, 990, 910 cm^{-1}; NMR (CCl_4 with Me_4Si) δ 1.17 (s, 18 H), 1.30 (s, 3 H), 1.72 (broad s, 3 H), 2.30 $\sim$ 2.60 (m, 2 H), 4.90 $\sim$ 5.40 (m, 2 H), 5.70 $\sim$ 6.30 (m, 2 H). Anal. ($C_{18}H_{30}O_2$) C, H. *E,E* stereochemistry of **36** and *E* stereochemistry of **37** were deduced from the NMR chemical shifts of olefinic protons and methyl protons on the sp^2 carbon.

Oxidative Dimerization of Phenyl *p*-Tolyl Ketone (31). Under a nitrogen atmosphere, diisopropylamine (5 mmol) in dry THF (8 ml) and hexamethylphosphoramide (2 ml) was treated with *n*-butyllithium (5 mmol) at −78 °C. After 15 min, 0.88 g (4.5 mmol) of phenyl *p*-tolyl ketone (**31**) (4.5 mmol) in THF (3 ml) was added dropwise with stirring to the solution. After 15 min, anhydrous $CuCl_2$ (5 mmol) in DMF (7.5 ml) was added at once at the same temperature. The dark-green solution was stirred for an additional 30 min and then allowed to reach room temperature. The reaction mixture was worked up with acid and extracted with chloroform. 1,2-Di(4-benzoylphenyl)ethane (**38**) (420 mg, 48%) was isolated by column chromatography (silica gel, benzene); TLC R_f 0.6, benzene. **38** was identified by comparison of its spectral data and melting point (mp 175 $\sim$ 176 °C) with those of an authentic sample.[21]

Oxidative Dimerization of (*E*)-Ethyl Crotonate (32). Under a nitrogen atmosphere, a solution of diisopropylamine (5 mmol) in THF (8 ml) and HMPA (2 ml) was treated with *n*-butyllithium (5 mmol) at −78 °C. After 15 min, 0.52 g (4.5 mmol) of (*E*)-ethyl crotonate (**32**) in THF (3 ml) was added dropwise with stirring to the solution. After 15 min, $CuCl_2$ (5 mmol) in DMF (7.5 ml) was added at once at the same temperature. Products of **39** (138 mg) and **40** (204 mg) were separated and isolated by preparative TLC (silica gel, $CHCl_3$); TLC, **39:** R_f 0.4, chloroform, **40:** R_f 0.6 chloroform. **39:** IR (neat) 1720, 1650 cm^{-1}; NMR (CCl_4 with Me_4Si) δ 1.25 (t, 6 H), 2.20 $\sim$ 2.50 (m, 4 H), 4.07 (q, 4 H) 5.66 (d, J = 15.0 Hz, 2 H), 6.40 $\sim$ 7.00 (m, 2 H). Anal. ($C_{12}H_{18}O_4$) C, H. **40:** IR (neat) 1730, 1655 cm^{-1}; NMR (CCl_4 with Me_4Si) δ 1.21 (t, 6 H) 2.10 $\sim$ 2.70 (m, 2 H), 2.70 $\sim$ 3.30 (m, 1 H), 4.05 (q, 4 H), 4.80 $\sim$ 6.00 (m, 4 H), 7.68 (dt, J = 16.2 Hz and J = 6.6 Hz, 1 H). Anal. ($C_{12}H_{18}O_4$) C, H.

By a similar procedure, oxidative dimerization of (*E*)-ethyl α-methylcrotonate (**33**) was carried out. Products of **41** and **42** were separated and isolated by preparative TLC (silica gel, 1:1 hexane–chloroform); TLC, **41:** R_f 0.5, 1:1 hexane–chloroform, **42:** R_f 0.7, 1:1 hexane–chloroform. **41:** IR (neat) 1710, 1650 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 1.27 (t, 6 H), 1.81 (d, J = 0.9 Hz, 6 H), 1.20 $\sim$ 1.40 (m, 4 H), 4.15 (q, 4 H), 6.40 $\sim$ 6.80 (m, 2 H). Anal. ($C_{14}H_{22}O_4$) C, H. **42:** IR (neat) 1730, 1715 cm^{-1}; NMR (CCl_4 with Me_4Si) δ 1.21 (two t, 6 H) 1.22 (s, 3 H), 1.77 (d, J = 1.0 Hz, 3 H) 2.44 (d, J = 7.2 Hz, 2 H), 4.08 (two q, 4 H), 4.80 $\sim$ 5.20 (m, 2 H), 5.60 $\sim$ 6.20 (m, 1 H), 6.48 (tq, J = 7.2 Hz and J = 1.0 Hz, 1 H). Anal. ($C_{14}H_{22}O_4$) C, H. *E,E* stereochemistry of **41** and *E* stereochemistry of **42** were determined by their NMR chemical shifts of olefinic protons.

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(32) The authors express their gratitude to Professor H. Nozaki, Kyoto University, for his generous donation of IR and NMR spectra of *cis*-jasmone and allyl rethrone.