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Studies on Organic Fluorine Compounds. XXXI.[1] Oxidative Coupling of Ketone Enolates and Trimethylsilyl Enol Ethers by Means of $Cu(OTf)_2$[2]

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The oxidative coupling of ketone enolates and trimethylsilyl enol ethers by means of cupric trifluoromethanesulfonate [$Cu(OTf)_2$] is described in detail. 1,4-Diketones were effectively prepared by treating lithium enolates with $Cu(OTf)_2$ in i-PrCN. 1,3-Cyclopentanedione derivatives were synthesized through intramolecular coupling of 2,4-pentanedione derivatives. Treatment of trimethylsilyl enol ethers with $Cu(OTf)_2$ in i-PrCN also afforded the corresponding coupling products.

Keywords——Oxidative coupling; cupric trifluoromethanesulfonate; 1,4-diketones; 1,3-cyclopentanediones; trimethylsilyl enol ether

1,4-Diketones are versatile intermediates for the synthesis of natural products and related compounds having a cyclopentenone or furan ring system.[4,5] Many synthetic routes to 1,4-diketones have been reported.[6] We recently reported an efficient synthesis of 1,4-diketones by oxidative coupling of ketone enolates and trimethylsilyl enol ethers, using cupric trifluoromethanesulfonate[$Cu(OTf)_2$].[7] This method has also been applied to the synthesis of 1,3-cyclopentanedione derivatives *via* intramolecular oxidative coupling of the lithium dienolates of 2,4-pentanediones.[8] In this paper, we describe in detail the oxidative coupling of ketone enolates and trimethylsilyl enol ethers by means of $Cu(OTf)_2$.

(A) Oxidative Coupling of Ketone Enolates

Transition metal-promoted dimerization of carbanions is a convenient method for carbon–carbon bond formation in organic synthesis. However, only one method for synthesizing 1,4-diketones through the dimerization of ketone enolates has been reported by Saegusa and his co-workers, and this involved treating ketone enolates in tetrahydrofuran (THF) at −78° with $CuCl_2$ in dimethylformamide (DMF).[6] Using their method, methyl ketones were dimerized to the desired 1,4-diketones in good yields, but an increase in alkyl substitution at the coupling site resulted in a substantial reduction in the yield of 1,4-diketones. As mentioned in our preliminary paper,[7] 1,4-diketones were found to be effectively prepared by the oxidative dimerization of ketone enolates generated *in situ* at −78° from the parent ketones and lithium diisopropylamide (LDA) in THF with $Cu(OTf)_2$ in isobutyronitrile (i-PrCN), even in the cases of ketones possessing alkyl substituents at the coupling site, as

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[2] A part of this work was presented at the 98th Annual Meeting of the Pharmaceutical Society of Japan, Okayama, April, 1978.

[3] Location: *Horinouchi, Hachioji, Tokyo 192-03, Japan.*

[4] *a*) R.A. Ellison, *Synthesis*, **1973**, 397; *b*) T.L. Ho, *Synth. Commun.*, **4**, 265 (1974).

[5] P. Bosshard and C.H. Eugster, *Adv. Heterocycl. Chem.*, **77**, 377 (1966).

[6] Y. Ito, T. Konoike, T. Harada, and T. Saegusa, *J. Am. Chem. Soc.*, **99**, 1487 (1977) and references cited therein.

[7] Y. Kobayashi, T. Taguchi, and E. Tokuno, *Tetrahedron Lett.*, **1977**, 3741.

[8] Y. Kobayashi, T. Taguchi, and T. Morikawa, *Tetrahedron Lett.*, **1978**, 3555.

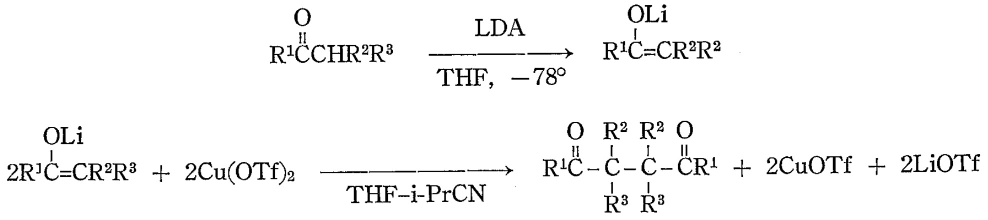
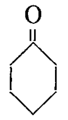
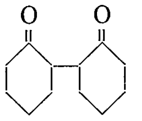
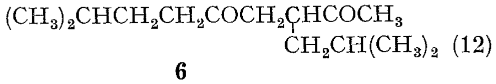


Chart 1

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

No.	Starting ketone	1,4-Diketones (Yield %)
1	$CH_3COC_6H_5$	$C_6H_5COCH_2CH_2COC_6H_5$ (83) **1**
2	$CH_3CH_2COC_6H_5$	$C_6H_5COCH(CH_3)CH(CH_3)COC_6H_5$ (80) **2**
3	$CH_3CH_2COCH_2CH_3$	$CH_3CH_2COCH(CH_3)CH(CH_3)COCH_2CH_3$ (63) **3**
4		 (73) **4**
5	$(CH_3)_2CHCH_2CH_2COCH_3$	$[(CH_3)_2CHCH_2CH_2COCH_2]_2$ (64) **5**  $(CH_3)_2CHCH_2CH_2COCH_2\underset{CH_2CH(CH_3)_2}{CH}COCH_3$ (12) **6**

shown in Table I. The use of $Cu(OTf)_2$ in i-PrCN for the oxidative coupling of ketone enolates to 1,4-diketones seems to be effective for the following reasons: a) a rapid displacement reaction of lithium enolate occurs with $Cu(OTf)_2$ to form the cupric enolate due to the effectiveness of the trifluoromethanesulfonoxy group (OTf) as a leaving group and the solubility of $Cu(OTf)_2$ in i-PrCN, b) the role of the nitrile group of i-PrCN as a ligand makes it easier to reduce the cupric enolate to Cu(I)OTf.9) However, further studies are required on the mechanism.

(B) Intramolecular Oxidative Coupling of Dienolates of Diketones and Diesters

As an extension of the present oxidative coupling of ketone enolates, we examined the intramolecular oxidative coupling of dienolates of diketones and diesters, which may yield cyclic compounds, such as cyclic 1,4-diketones or cycloalkane-1,2-dicarboxylic acid derivatives.

First, we attempted the oxidative coupling of dilithium enolates of 3,3-dialkyl-2,4-pentanediones with $Cu(OTf)_2$ for the preparations of 2,2-dialkyl-1,3-cyclopentanediones and functionalized spiro[4, *n*]ring systems, as shown in Chart 2. Though 1,3-cyclopentanedione derivatives are potentially useful synthetic intermediates,4,10) alkylation of 1,3-cyclopentanedione with alkyl halides gives unsatisfactory results due to the competitive O-alkylation.11)

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9) T. Cohen and I. Cristea, *J. Am. Chem. Soc.*, **98**, 748 (1976).

10) A.P. Krapcho, *Synthesis*, **1974**, 383; **1976**, 425; **1978**, 77.

11) *a*) D.J. Crispin, A.E. Vanstone, and J.S. Whitehurst, *J. Chem. Soc.* (*C*), **1970**, 10; *b*) W.A. Agosta and A.B. Smith, III, *J. Org. Chem.*, **35**, 3856 (1970).

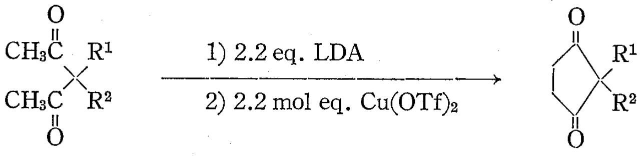

Chart 2

Treatment of 3,3-dialkyl-2,4-pentanedione with 2.2 eq. of LDA in THF at −78° and subsequent addition of 2.2 mol eq. of $Cu(OTf)_2$ in i-PrCN afforded the corresponding coupling product in 21—28% yield (Method A). To minimize the competitive intermolecular coupling, we examined the reverse addition of the THF solution of the dienolate to $Cu(OTf)_2$ in THF and i-PrCN at −78° (Method B), which resulted in a slight increase in the yield of the desired coupling product, as shown in Table II.[12] Though the yields are not very good, the procedure is a simple "one-pot" reaction and the starting materials are readily available.

Treatment of dienolates of 1,3-dibenzoylpropane and 1,4-dibenzoylbutane with $Cu(OTf)_2$ gave the corresponding cyclopropane[13] and cyclobutane,[14] respectively.

Intramolecular oxidative coupling of dienolates of diesters was also examined, and the corresponding cyclopropane (**13**)[15] and cyclohexane (**14**)[16] derivatives were successfully obtained; diethyl pimelate (n=5) could not be converted to its dienolate, but gave the intramolecular ester condensation product (**15**) in 51% yield[17] as shown in Chart 3. The results of intramolecular oxidative coupling of dienolates of diketones and diesters are summarized in Table 2.

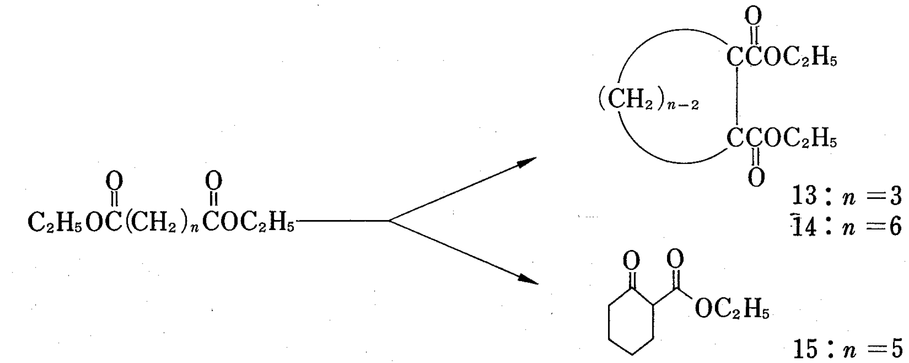

Chart 3

(C) Oxidative Coupling of Trimethylsilyl Enol Ether

As described in the previous paper,[7] treatment of trimethylsilyl enol ether[18] with $Cu(OTf)_2$ in the presence of Cu_2O in i-PrCN afforded the corresponding 1,4-diketone (Chart 4). The following features of this coupling reaction are noteworthy. a) The use of i-PrCN as a solvent was crucial in this reaction. When acetonitrile was used as a solvent, the 1,4-diketone (**1**) was obtained in nearly the same yield, but a small amount of a by-product containing a nitrile group was also obtained. With dimethylformamide (DMF), dimethylsulfoxide (DMSO) or hexamethylphosphorictriamide (HMPA) as a solvent, the 1,4-diketone

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[13] G.W. Griffin, E.J. O'Connell, and H.A. Hammond, *J. Am. Chem. Soc.*, **85**, 1001 (1963).
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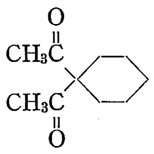
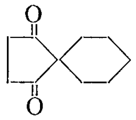
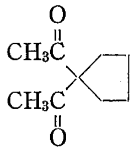
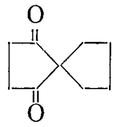
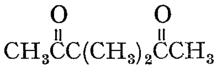
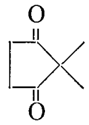
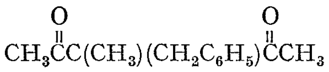
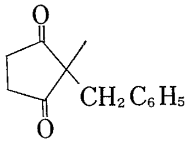
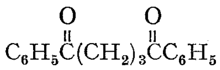
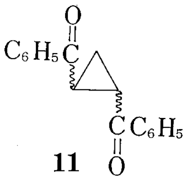
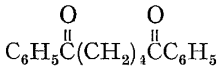
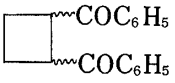
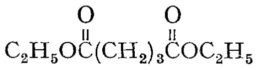
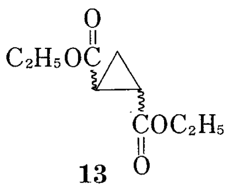
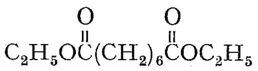
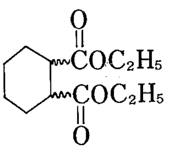
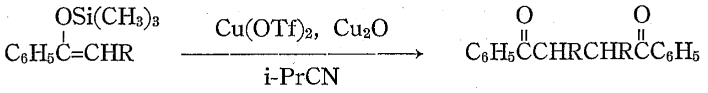
[15] M. Mousseron, R. Fraisse, R. Jacquier, and G. Bonavent, *Compt. rend.*, **248**, 2840 (1959).
[16] C.C. Price and M. Schwarcz, *J. Am. Chem. Soc.*, **62**, 2891 (1940).
[17] J.P. Schaefer, "Organic Reactions," Vol. 15, ed. by A.C. Cope, John Wiley and Sons, Inc., New York, 1967, p. 1.
[18] H.O. House, L.J. Czuba, M. Gall, and H.D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969).

Table II. Intramolecular Oxidative Coupling of Dienolates of Diketones and Diesters

No.	Starting material	Mathod	Product	(Yield %)
1		A	 **7**	(25)
2		B	**7**	(47)
3		B	 **8**	(27)
4	 $\mathrm{CH_3\overset{\underset{\|}{O}}{C}C(CH_3)_2\overset{\underset{\|}{O}}{C}CH_3}$	A	 **9**	(28)
5		B	**9**	(32)
6	 $\mathrm{CH_3\overset{\underset{\|}{O}}{C}C(CH_3)(CH_2C_6H_5)\overset{\underset{\|}{O}}{C}CH_3}$	A	 **10**	(21)
7		B	**10**	(38)
8	 $\mathrm{C_6H_5\overset{\underset{\|}{O}}{C}(CH_2)_3\overset{\underset{\|}{O}}{C}C_6H_5}$	A	 **11**	(48)
9	 $\mathrm{C_6H_5\overset{\underset{\|}{O}}{C}(CH_2)_4\overset{\underset{\|}{O}}{C}C_6H_5}$	A	 **12**	(15)
10	 $\mathrm{C_2H_5O\overset{\underset{\|}{O}}{C}(CH_2)_3\overset{\underset{\|}{O}}{C}OC_2H_5}$	A	 **13**	(62)
11	 $\mathrm{C_2H_5O\overset{\underset{\|}{O}}{C}(CH_2)_6\overset{\underset{\|}{O}}{C}OC_2H_5}$	A	 **14**	(38)



$$C_6H_5\overset{OSi(CH_3)_3}{C}{=}CHR \xrightarrow[\text{i-PrCN}]{Cu(OTf)_2,\ Cu_2O} C_6H_5\overset{O}{\overset{\|}{C}}CHRCHR\overset{O}{\overset{\|}{C}}C_6H_5$$

Chart 4

was obtained in only a trace amount, and the starting silyl enol ether was recovered. b) In the absence of Cu_2O the reaction of the silyl enol ether with $Cu(OTf)_2$ gave complex products, including a trace amount of 1,4-diketone. Cu_2O was more effective than CuO for this coupling reaction. c) Other Cu(II) salts such as $Cu(O_2CCF_3)_2$, $CuCl_2$ and CuO were not effective. The reaction of silyl enol ether with $CuCl_2$ in CH_3CN gave α-chloroacetophenone in 37% yield, with recovery of acetophenone (50%) after aqueous work-up.[19] d) An increase in alkyl substitution at the coupling site resulted in a reduction in the yield of 1,4-diketone, as in the case of the trimethylsilyl enol ether of propiophenone (27% yield). These results are summarized in Table 3.

TABLE III. Oxidative Coupling of 2-Trimethylsiloxystyrene (**16**)

Cu (II) Salt	Additive	Solvent	Temp (°C)	Time (hr)	Yield of **1** (%)
Cu $(OTf)_2$	Cu_2O	*i*-PrCN	0°	2	55
Cu $(OTf)_2$	Cu_2O	CH_3CN	0°	2.5	57
Cu $(OTf)_2$	CuO	CH_3CN	0°	2.5	37
Cu $(OTf)_2$	—	CH_3CN	r. temp.	0.5	5
Cu $(OTf)_2$	Cu_2O	DMF	75—80°	6	Trace
Cu $(OTf)_2$	Cu_2O	HMPA	100°	6	Trace
Cu $(OTf)_2$	Cu_2O	DMSO	80°	6	Trace
$Cu(O_2CCF_3)_2$	Cu_2O	CH_3CN	r. temp.	4	Trace
$CuCl_2$	Cu_2O	CH_3CN	r. temp.	24	0
CuO	—	CH_3CN	r. temp.	24	0

In conclusion, the $Cu(OTf)_2$–i-PrCN system is an effective reagent for the oxidative coupling of ketone enolates and trimethylsilyl enol ethers to the corresponding 1,4-diketones. Furthermore, successful applications of this coupling reaction for intramolecular systems show that it is a potentially useful synthetic reaction in view of its use of readily available starting materials and its simple procedure.

Experimental

Oxidative Coupling of Ketone Enolate, General Procedure——A solution of diisopropylamine (2.2 mmol) in THF (6 ml) was treated with *n*-butyllithium (2.2 mmol, 10% hexane solution) under an argon atmosphere at −78°, and after 10 min, a solution of ketone (2 mmol) in THF (4 ml) was added to the resulting THF solution of LDA. After 15 min, 800 mg (2.2 mmol) of anhydrous $Cu(OTf)_2$ (which had been dried at 110—120° for 1 hr under reduced pressure (5 mmHg) prior to use) dissolved in i-PrCN (2 ml) was added to the THF solution of the ketone enolate at −78°. The dark-brown solution was stirred for 30 min at −78° and then for a further 30 min at room temperature. The reaction mixture was treated with *d*-HCl and extracted with ether. The organic layer was washed with brine and dried over $MgSO_4$. The ether solution was concentrated *in vacuo* and chromatographed on silica gel. Further purification was performed by distillation or recrystallization.

1,4-Diphenyl-1,4-butanedione (1)——83% yield. mp 148—149° (lit.[20] 145—147°). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1678. NMR ($CDCl_3$) δ 3.47 (4H, s, methylene H), 8.10 (4H, m, arom. H), 7.50 (6H, m, arom. H). MS *m/e* 238 (M^+). *Anal.* Calcd for $C_{16}H_{14}O_2$: C, 80.64; H, 5.92. Found: C, 80.69; H, 6.00.

***dl* and *meso* 2,3-Dimethyl-1,4-diphenyl-1,4-butanedione (2)**——Total 80% yield: less polar material, 20% yield. mp 98—99°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1675. NMR (CCl_4) δ 1.10 (6H, d, J=7 Hz, methyl H), 4.00 (2H, dq, J=7, 2 Hz, methine H), 7.46 (6H, m, arom. H), 8.02 (4H, m, arom. H). MS *m/e* 105, 77, 56. *Anal.*

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[19] E.M. Kosower, W.J. Cole, G.-S. Wu, D.E. Cardy, and G. Meisters, *J. Org. Chem.*, **28**, 630 (1963).

[20] P.S. Bailey and R.E. Lutz, *J. Am. Chem. Soc.*, **70**, 2412 (1948).

Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 80.87; H, 6.83. more polar material, 60% yield. mp 84—85°. IR ν_{max}^{KBr} cm^{-1}: 1680. NMR (CCl_4) δ 1.20 (6H, d, $J=7$ Hz, methyl H), 3.90 (2H, dq, $J=7$, 3 Hz, methine H), 7.36 (6H, m, arom. H), 7.90 (4H, m, arom. H). MS *m/e* 105, 77, 56. *Anal.* Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 80.89; H, 6.89.

***dl* and *meso* 4,5-Dimethyl-3,6-octanedione** (**3**)——63% yield. bp 78—80° (3 mmHg) (bulb-to-bulb distillation). IR ν_{max}^{KBr} cm^{-1}: 1705. NMR (CCl_4) δ 0.96 (6H, t), 1.00 (6H, m), 2.46 (4H, m, methylene H), 2.78 (2H, m, methine H). MS *m/e* 171 (M^+, +1), 170 (M^+), 141, 113, 57.

Oxidative Coupling of Cyclohexanone[21]——**4**, 73% yield. bp 128—135° (7 mmHg) (bulb-to-bulb distillation). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1705. MS *m/e* 194 (M^+), 176 ($M^+ - H_2O$), 148, 98. *Anal.* Calcd for $C_{12}H_{18}O_2$: C, 74.12; H, 9.34. Found: C, 74.05; H, 9.22.

Oxidative Coupling of 5-Methyl-2-hexanone——**5**, 64% yield. bp 128—135° (3 mmHg) (bulb-to-bulb distillation). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1705. NMR (CCl_4) δ 0.88 (12H, d, $J=7$ Hz), 1.40—1.70 (6H, m), 2.40 (4H, t, $J=8$ Hz, $-\overset{\overset{O}{\|}}{C}C\underline{H}_2-CH_2CH(CH_3)_2$), 2.57 (4H, s, $-\overset{\overset{O}{\|}}{C}C\underline{H}_2C\underline{H}_2\overset{\overset{O}{\|}}{C}-$). MS *m/e* 227 ($M^+$ +1), 226 (M^+), 155, 127, 114, 99. *Anal.* Calcd for $C_{14}H_{26}O_2$: C, 74.28; H, 11.58. Found: C, 74.43; H, 11.80. **6**, 12% yield. bp 137—140° (7 mmHg) (bulb-to-bulb distillation). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1705. NMR (CCl_4) δ 0.84—0.96 (12H, m), 1.20—1.70 (6H, m), 2.17 (3H, s, $-\overset{\overset{O}{\|}}{C}C\underline{H}_3$), 2.33 (2H, t, $J=7$ Hz, $-\overset{\overset{O}{\|}}{C}C\underline{H}_2CH_2CH(CH_3)_2$), 2.70 (2H, d, $J=9$ Hz, $-\overset{\overset{O}{\|}}{C}C\underline{H}_2CH\langle_{Ac}$), 2.92 (1H, m, ${}^{Ac}\rangle C\underline{H}CH_2\overset{\overset{O}{\|}}{C}-$). MS *m/e* 227 ($M^+$ +1), 226 (M^+), 183, 170, 155, 114, 99. *Anal.* Calcd for $C_{14}H_{26}O_2$: C, 74.28; H, 11.58. Found: C, 74.15; H, 11.86.

Oxidative Coupling of 3,3-Dimethyl-2,4-penanedione (Method A)——A solution of 4.4 mmol of LDA in THF (10 ml) was treated with 256 mg (2 mmol) of 3,3-dimethyl-2,4-pentanedione in THF (15 ml) under an argon atmosphere at −78°. After 15 min, 1.5 g (4.1 mmol) of $Cu(OTf)_2$ dissolved in 4 ml of i-PrCN was added at once to the THF solution of the dienolate. The dark-brown solution was stirred at −78° for 30 min and then allowed to warm up to room temperature. The reaction mixture was treated with d-HCl and extracted with ether. The organic layer was washed with brine and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica gel. The fraction eluted with dichloromethane gave 72 mg (28%) of **9**, which was identical (IR, NMR and MS) with an authentic sample.[11a)]

Oxidative Coupling of Diethyl Suberate——Using the procedure described above (Method A), oxidative coupling of 182 mg of diethyl suberate with $Cu(OTf)_2$ gave 70 mg (38%) of **14** as a colorless oil. bp 100° (2 mmHg) (bulb-to-bulb distillation). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1740. High-resolution MS *m/e* Calcd for $C_{12}H_{20}O_4$: 228.1361. Found: 228.1344.

Oxidative Coupling of 1,1-Diacetylcyclohexanone (Method B)——A solution of LDA (2.64 mmol) in THF (3 ml) was treated with 202 mg (1.2 mmol) of 1,1-diacetylcyclohexanone in THF (3 ml) under an argon atmosphere at −78°. After 10 min, the cooling bath was removed. In another two-necked flask fitted a serum cap, a solution of 724 mg (2 mmol) of $Cu(OTf)_2$ in i-PrCN (2 ml) and THF (10 ml) was cooled at −78°. The dienolate solution was added dropwise to this solution with a syringe, and the resulting dark-brown solution was stirred at −78° for 30 min, then allowed to warm up to room temperature. The reaction mixture was treated with d-HCl and extracted with ether. The organic layer was washed with brine and dried over $MgSO_4$. The ether solution was concentrated *in vacuo* and chromatographed on silica gel. The fraction eluted with dichloromethane and *n*-hexane (2:1 v/v) gave 80 mg (47%) of **7** as colorless needles; this material was recrystallized from *n*-hexane. mp 64.5—66°. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1710. NMR (CCl_4) δ 1.63 (10H, s), 2.77 (4H, s). MS *m/e* 164 (M^+). *Anal.* Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.32; H, 8.44.

Oxidative Coupling of 1,1-Diacetylcyclopentane——Using the procedure described above (Method B), oxidative coupling of 154 mg of 1,1-diacetylcyclopentane with $Cu(OTf)_2$ gave 41 mg (27%) of **8** as colorless needles; this material was recrystallized from *n*-hexane. mp 65—66.5°. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1720. NMR (CCl_4) δ 1.80 (8H, s), 2.70 (4H, s). MS *m/e* 152 (M^+). *Anal.* Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.61; H, 8.01.

Oxidative Coupling of 2-Trimethylsiloxystyrene——A solution of 400 mg (1.1 mmol) of $Cu(OTf)_2$ and 572 mg (4 mmol) of Cu_2O in i-PrCN (1 ml) was treated with a solution of 192 mg (1 mmol) of 2-trimethylsiloxystyrene in i-PrCN (1 ml) under an argon atmosphere at 0°. After 2 hr, the reaction mixture was diluted by the addition of water (5 ml) and ether (15 ml) and the whole was stirred for about 10 min. The resulting precipitate was filtered off. The filtrate was extracted with ether and the organic layer was washed with brine, then dried over $MgSO_4$. After removal of the solvent *in vacuo*, the residue was chromatographed on silica gel. The fraction eluted with dichloromethane–*n*-hexane (1:1 v/v) gave 64 mg (55%) of **1** as colorless crystals, mp 148—149°.

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21) M.S. Kharasch, H.C. McBay, and W.H. Urry, *J. Am. Chem. Soc.*, **70**, 1269 (1948).