Chemoselective Coupling of α-Bromo Aldehydes with a Tin Enolate Derived from the Ring Opening of Diketene by Bis(tributyltin) Oxide

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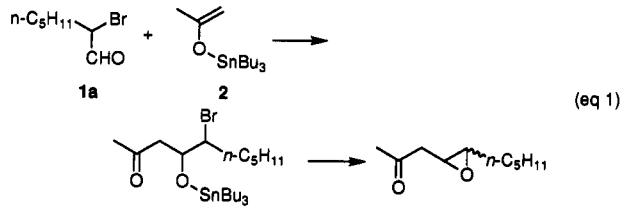
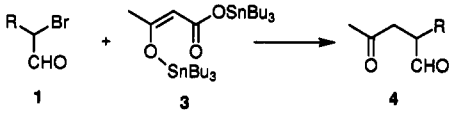
Organotin enolates[1] are widely used for mild and effective carbon–carbon bond formation in reactions with various electrophiles such as carbonyl compounds[2] and alkyl halides.[3] In the reaction of tin enolates with α-halo ketones, the main products are generally derived from nucleophilic addition to the carbonyl group.[4] For example, thermal reactions[4a] and Pd-catalyzed reactions[4b] give furan derivatives and β-epoxy ketones, respectively. The occurrence of cross coupling at the halide moiety is limited to bromopinacolone[5a] and bromo esters.[5b] We have recently reported that Lewis base-coordinated organotin enolates chemoselectively cross couple at the halide moiety of α-halo ketones to furnish 1,4-diketones, even with halo acetone derivatives.[6] This change in chemoselectivity is thought to arise from the fact that the tin enolates are highly coordinated. One disturbing problem remains: the halide-selective coupling cannot be accomplished with α-halo aldehydes. For example, the reaction of 2-bromoheptanal (**1a**) with tributyltin enolate **2** gave a β-ketooxirane even in the presence of HMPA; exclusive carbonyl addition was followed by the elimination of Bu_3SnBr[6b] (eq 1). In contrast, as demonstrated in our recent



(eq 1)

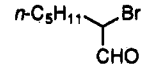
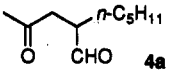
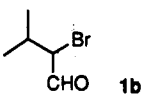
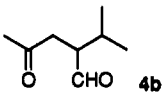
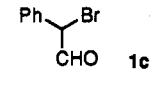
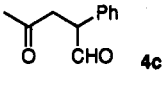
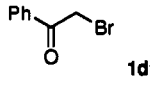
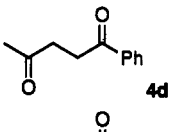
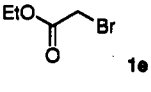
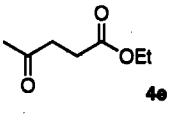
report, a novel tin enolate **3**, generated by the ring opening of diketene with bis(tributyltin) oxide [$(Bu_3Sn)_2O$],[7] induced effective Michael addition,[8] which rarely occurs with conventional organotin enolates. This unique reactivity can be ascribed to the intramolecular coordination of the carbostannyloxy group to the enolate tin center. We have now found that enolate **3** participates in a valuable chemoselective cross coupling at the bromide moiety of α-bromo aldehydes (eq 2).



(eq 2)

Table 1 summarizes the coupling reactions of **3**, which was easily prepared *in situ* at 0 °C for 10 min. First, we examined the reaction of **3** with 2-bromoheptanal (**1a**) at 40 °C for 24 h. During the reaction, decarboxylation was observed, and keto aldehyde **4a** was obtained in 40% yield (entry 1). It is noteworthy that the reaction proceeded only at the bromide moiety, and no products derived from addition to the carbonyl moiety were produced. This dramatic change in chemoselectivity indicates that the intramolecular coordination in **3** changes the nucleophilicity of the tin enolate more effectively than does the intermolecular coordination of HMPA to tin enolate **2**.[6] Moreover, the use of LiBr as an additive accelerated the reaction, and keto aldehyde **4a** could be obtained in 74% yield at rt for 2 h (entry 2). Similarly, a bromo aldehyde bearing a branched substituent, **1b**, and an aromatic substrate, **1c**, also gave the corresponding keto aldehydes, **4b** and **4c**, respectively (entries 3 and 4). In all entries examined, no adducts derived from carbonyl addition were obtained. As expected, α-bromo ketone **1d** and α-bromo

Table 1. Preparation of Methyl Ketone Derivatives by the Alkylation of 3[a]

entry	bromocarbonyls (1)	condns	product (4)	yield[b] (%)
1	 **1a**	40 °C, 24 h	 **4a**	40[c]
2		rt, 2 h		74
3	 **1b**	rt, 24 h	 **4b**	77
4	 **1c**	rt, 24 h	 **4c**	44
5	 **1d**	rt, 24 h	 **4d**	80
6	 **1e**	rt, 8 h	 **4e**	85

[a] Enolate **3** was prepared in situ by the reaction of diketene (2 mmol) and $(Bu_3Sn)_2O$ (2 mmol) at 0 °C for 10 min. Alkylation step: bromo carbonyl **1**, 2 mmol, LiBr, 2 mmol, THF, 2 mL. [b] Isolated yield. [c] Without LiBr.

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(2) (a) Noltes, J. G.; Creemers, H. M. J. C.; Van Der Kerk, G. J. M. *J. Organomet. Chem.* **1968**, *11*, 21. (b) Labadie, S. S.; Stille, J. K. *Tetrahedron* **1984**, *40*, 2329. (c) Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1981**, 162. (d) Kobayashi, K.; Kawanishi, M.; Hitomi, T.; Kojima, S. *Chem. Lett.* **1983**, 851. (e) Shibata, I.; Yamasaki, H.; Baba, A.; Matsuda, H. *J. Org. Chem.* **1992**, *57*, 6909. (f) Shibata, I.; Yamaguchi, T.; Baba, A.; Matsuda, H. *Chem. Lett.* **1993**, 97.

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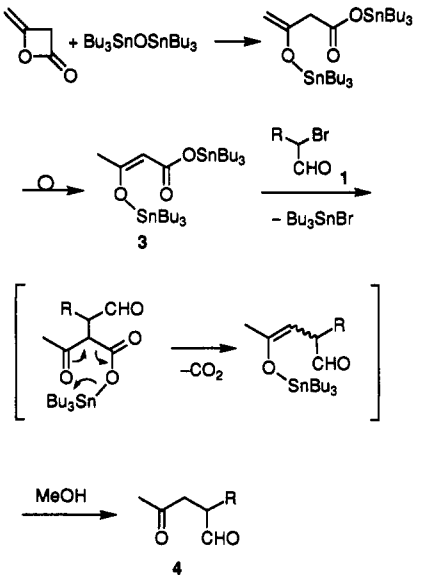
(6) (a) Baba, A.; Yasuda, M.; Yano, K.; Shibata, I.; Matsuda, H. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3205. (b) Yasuda, M.; Oh-hata, T.; Shibata, I.; Baba, A.; Matsuda, H. *J. Chem. Soc., Perkin Trans. 1* **1993**, 859.

(7) Shibata, I.; Nishio, M.; Baba, A.; Matsuda, H. *Chem. Lett.* **1993**, 1219.

(8) Shibata, I.; Nishio, M.; Baba, A.; Matsuda, H. *J. Chem. Soc., Chem. Commun.* **1993**, 1067.

0022-3263/94/1959-0486$04.50/0

Scheme 1



ester **1e** undergo chemoselective reaction at the bromide moiety to furnish 1,4-diketones, **4d** and **4e**, respectively, in good yields (entries 5 and 6). Obviously, enolate **3** is a synthon of enolate **2**.

The reaction path is detailed in Scheme 1. Initially, regioselective ring opening of diketene takes place at the acyl–oxygen bond to afford an *exo*-methylene-type tin enolate, which isomerizes to stable enolate **3**. Next, enolate **3** exclusively attacks the bromide moiety of **1**, and this attack is accompanied by smooth decarboxylation.[9] Finally, keto aldehyde **4** is formed when the reaction mixture is quenched with MeOH.

In summary, chemoselective carbon–carbon bond formation was performed with tin enolate **3** derived from diketene. The presented method expands not only organotin chemistry but also the utility of diketene.

Experimental Section

Analysis. Boiling points are uncorrected. NMR spectra were recorded at 400 MHz. Samples were examined in deuteriochloroform ($CDCl_3$) containing 0.03% by volume of TMS. GLC analyses were performed on a FFAP-coated 2-m × 3-mm glass column. Column chromatography was performed with Wakogel C-200 or C-300 mesh silica gel. Preparative TLC was carried out on Wakogel B-5F mesh silica gel.

Materials. Bis(tri-*n*-butyltin) oxide [$(Bu_3Sn)_2O$], diketene, bromo ketone **1d**, and bromo ester **1e** were commercially available. α-Bromo aldehydes **1a–1c** were prepared by the bromination of the corresponding aldehydes.[10]

4-Formylnonan-2-one (4a). General Procedure for the Preparation of Keto Aldehydes. Diketene (0.174 g, 2 mmol) was added to a solution of 1.19 g of $(Bu_3Sn)_2O$ (2 mmol) in THF (2 mL), and the mixture was stirred at 0 °C for 10 min. The disappearance of the IR absorption band of diketene at 1900 cm^{-1} indicated that the ring opening of diketene to form enolate **3** had occurred. Then 0.39 g of 2-bromoheptanal (**1a**) (2 mmol) and 0.17 g of LiBr (2 mmol) were successively added, and the mixture was stirred at rt for 2 h. After the mixture was quenched with MeOH (5 mmol), the solvent was removed under reduced pressure. The residue was subjected to column chromatography with 1:1 hexane/ethyl acetate to give 0.25 g of **4a** (74%). Further purification was performed by TLC with 2:1 hexane/ethyl ether: IR (neat) 1710, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 7.0 Hz, CH_3), 1.25–1.70 (m, 8H, CH_2), 2.19 (s, 3H, $CH_3C{=}O$), 2.45 (dd, 1H, J = 8.0 and 21.3 Hz one of CH_2Ac), 2.83–2.93 (m, 2H, one of CH_2Ac and C*H*CHO), 9.70 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$) δ 13.78, 22.28, 26.55, 28.51, 29.93, 31.67, 42.13, 46.73, 203.21, 206.37; HRMS m/z calcd for $C_{10}H_{18}O_2$ 170.1307, found 170.1301.

4-Formyl-5-methylhexan-2-one (4b): IR (neat) 1710, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (d, 3H, J = 6.8 Hz, CH_3), 1.01 (d, 3H, J = 6.8 Hz, CH_3), 2.13–2.23 (m, 1H, $CHMe_2$), 2.21 (s, 3H, $CH_3C{=}O$), 2.34 (dd, 1H, J = 7.3 and 22.0 Hz, one of CH_2), 2.88–2.95 (m, 2H, one of CH_2 and C*H*CHO), 9.75 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$) δ 19.26, 20.35, 29.48, 30.90, 38.56, 52.59, 203.69, 206.97; HRMS m/z calcd for $C_8H_{14}O_2$ 142.0994, found 142.0990.

4-Formyl-4-phenylbutan-2-one (4c): IR (neat) 1710, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.19 (s, 3H, CH_3), 2.65 (dd, J = 4.9 and 18.1 Hz, CHPh), 3.36 (dd, 1H, J = 8.8 and 18.1 Hz, one of CH_2-Ac), 4.22 (dd, 1H, J = 4.9 and 8.8 Hz, one of CH_2Ac), 7.17–7.38 (m, 5H, Ph), 9.67 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$) δ 30.01, 43.59, 53.55, 127.79, 128.83, 129.17, 135.09, 198.79, 205.84; HRMS m/z calcd for $C_{11}H_{12}O_2$ 176.0837, found 176.0825.

The spectroscopic data for compounds **4d** and **4e** are consistent with those we have already reported.[8]

1-Phenylpentane-1,4-dione (4d): IR (neat) 1670, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.26 (s, 3H, CH_3), 2.89 (dd, 2H, J = 5.9 and 6.8 Hz, CH_2), 3.28 (dd, 2H, J = 5.9 and 6.8 Hz, CH_2), 7.20–8.00 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 30.10, 32.43, 37.07, 128.06, 128.59, 133.17, 136.65, 198.56, 207.39; HRMS m/z calcd for $C_{11}H_{12}O_2$ 176.0837, found 176.0854.

Ethyl 4-oxopentanoate (4e): IR (neat) 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (t, 3H, J = 7.1 Hz, $MeCH_2$), 2.20 (s, 3H, CH_3), 2.50–2.90 (m, 4H, CH_2), 4.15 (q, 1H, J = 7.1 Hz, $MeCH_2$); ^{13}C NMR ($CDCl_3$) δ 14.1, 28.0, 29.8, 37.9, 60.5, 172.5, 206.3; MS m/z 144 (M^+). Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.05; H, 8.45.

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Supplementary Material Available: Experimental details for compounds **4a–e** and ^1H and ^{13}C NMR spectra of **4a–c** (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(9) In contrast to 2-bromoheptanal (**1a**), the reaction of 2-chloroheptanal with **3** afforded the adduct derived from addition at the carbonyl group.[7]

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