

## Change of Regioselectivity in the Reaction of Tin Enolates and $\alpha$ -Bromo Ketones; Synthesis of 1,4-Diketones under Non-radical Conditions

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The reaction of tin enolates with  $\alpha$ -halogeno ketones, strikingly effected by the addition of phosphine oxides to the reaction mixture, produced 1,4-diketones under mild conditions; the addition was shown to proceed in a non-radical manner.

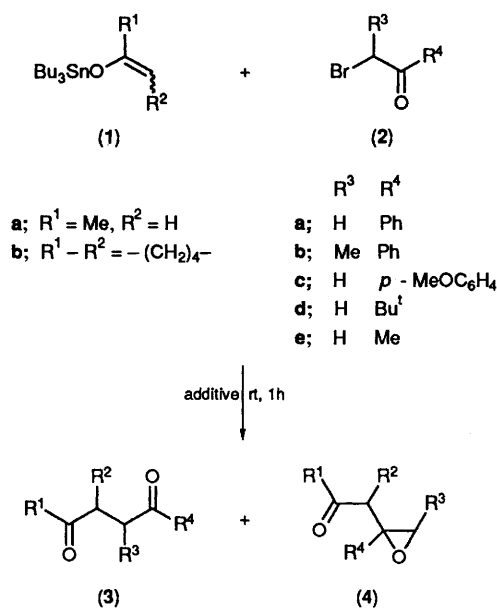
The reactions of metal enolates with numerous electrophiles have been much studied. In particular, tin enolates have attracted attention as versatile reagents because of their high reactivity and moderate stability.<sup>1</sup>  $\alpha$ -Halogeno ketones react as active electrophiles with tin enolates at either the carbonyl<sup>2</sup> or halide function.<sup>3</sup> The addition at the carbonyl moiety has been considered to be general, since oxirane derivatives are formed when the reaction mixtures are heated in the absence of additives; the reaction is catalysed by Pd.<sup>4</sup> In contrast, additions producing 1,4-diketones readily proceed under radical conditions, although the application of these reactions have been limited to bulky substituted halogeno ketones in the presence of a Ru-catalyst.<sup>3</sup> Thus, no general method for effective preparation of 1,4-diketones from tin enolates and  $\alpha$ -halogeno ketones has so far been reported.

Recently, we examined base-co-ordinated organotin compounds, where Sn-O, Sn-halogen, and Sn-H bonds were effectively activated by the co-ordination of phosphine oxides, phosphines, or amines.<sup>5</sup> In the course of our investigations, we observed a fine change of chemoselectivity upon addition of phosphine oxides to the reaction of tin enolates (1) with  $\alpha$ -halogeno ketones (2), in which a variety of 1,4-diketones (3) were produced in good yields.

Table 1 exemplifies the formation of compounds (3). For the halogeno ketones used, except for (2b) and (2d), these reactions proceeded exothermically at ambient temperature and were almost complete in <15 min. The reaction of (2a) is a typical case in which the effect of hexamethylphosphoric triamide (HMPT) addition is demonstrated since no addition took place in its absence at ambient temperature; at 80 °C however an oxirane derivative (4aa) was exclusively obtained. Of the additives investigated, tributylphosphine oxide and HMPT were effective whilst tertiary amines and phosphines were not. It is noteworthy that the high co-ordination ability of the former

compounds toward tin compounds is widely recognized.<sup>6</sup> Two types of representative tin enolates, (1a) and (1b), which are known to favour the keto and enol forms respectively,<sup>7</sup> were similarly found to react under mild conditions. Typical halogeno ketones such as (2a), (2b), and (2e), produced the corresponding 1,4-diketones in good yields. Thus, this method appears to be widely applicable.

A lower yield of (3aa) was obtained by adding a large excess



Scheme.

	$\text{R}^3$	$\text{R}^4$
<b>a;</b>	H	Ph
<b>b;</b>	Me	Ph
<b>c;</b>	H	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>
<b>d;</b>	H	Bu <sup>t</sup>
<b>e;</b>	H	Me

**a;**  $\text{R}^1 = \text{Me}$ ,  $\text{R}^2 = \text{H}$   
**b;**  $\text{R}^1 - \text{R}^2 = -(\text{CH}_2)_4-$

**Table 1.** Reaction of tin enolates with  $\alpha$ -bromo ketones<sup>a</sup>

Entry	Enolate	Halogeno ketone	Additives	Yield (%) and product
1	(1a)	(2a)	HMPT	73 (3aa), 12 (4aa)
2	(1a)	(2a)	HMPT (5 equiv.) <sup>b</sup>	33 (3aa), 0
3 <sup>c</sup>	(1a)	(2b)	HMPT	78 (3ab), 0
4 <sup>d</sup>	(1a)	(2c)	HMPT	67 (3ac), 0
5 <sup>e</sup>	(1a)	(2d)	HMPT	79 (3ad), 0
6	(1a)	(2e)	HMPT	59 (3ae), <sup>f</sup>
7	(1b)	(2a)	Bu <sub>3</sub> P=O	76 (3ba), 0
8	(1a)	(2a)	—	0, 0 (90) <sup>g</sup> (4aa)

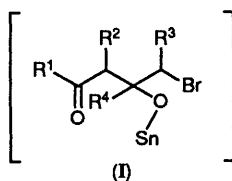
<sup>a</sup> Sn-Enolate/halogeno ketone/additive = 3.6/3.0/5.4 mmol, benzene 2 ml, room temp., 1 h. <sup>b</sup> 18 mmol. <sup>c</sup> 50 °C, 4 h. <sup>d</sup> A yield of 78% was obtained by the addition of Bu<sub>3</sub>P=O instead of HMPT. <sup>e</sup> 7 h. <sup>f</sup> The amount of oxirane could not be determined because of its instability. <sup>g</sup> The yield in parenthesis was obtained at 80 °C for 3 h.

**Table 2.** Reactions under radical conditions<sup>a</sup>

Entry	(2)	Additives	Conditions	Yield (%) <sup>b</sup> and product
1	(2a)	—	UV	65 (3aa), 0 (4aa)
2	(2a)	—	TEMPO UV	2 (3aa), 0 (4aa)
3	(2a)	HMPT	TEMPO <sup>c</sup>	62 (3aa), 13 (4aa)
4	(2a)	HMPT	Dark	59 (3aa), 13 (4aa)
5	(2b)	—	UV	13 (3ab), 0 (4ab)

<sup>a</sup> Sn-Enolate (1a)/halogeno ketone/HMPT/TEMPO = 3.6/3.0/5.4/0.3 mmol, benzene 2 ml, a Pyrex glass wear, a mercury lamp (250 W), 20 °C, 1 h. <sup>b</sup> GLC yield. <sup>c</sup> Instead of TEMPO, dinitrobenzene gave a similar result.

of HMPT, perhaps because excessive co-ordination of HMPT to (1) prevented interaction with (2); no oxirane derivative was formed (entry 2). On the other hand, a 0.1 equimolar amount of HMPT gave (3aa) (21%) and (4aa) (17%). These results strongly suggest that  $\alpha$ -halogeno ketones react with active five-co-ordinate tin enolates, to give, predominantly, 1,4-diketones.



A solution of (1a) and (2a) when irradiated in benzene with a 250-W high-pressure mercury lamp (see Table 2) gave only the 1,4-diketone (3aa) (65%); however, in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), a radical inhibitor, formation of the latter was much depressed. This suggests that the reaction is a radical one. In contrast, neither TEMPO nor *p*-dinitrobenzene affected the reaction in the presence of HMPT, 59% of 1,4-diketone being produced in the absence of light. These results suggest that the addition of HMPT changes the path of diketone formation into a non-radical one. In contrast to the reaction of (2a), 2-bromopropiophenone (2b) gave the corresponding 1,4-diketone (3ab) in 13% yield under radical conditions (Table 2, entry 5), and 78% yield in the presence of HMPT (Table 1, entry 3). This result demonstrates the versatility of the phosphine oxide-activated method.

In the absence of additives, neither oxirane nor 1,4-diketone were obtained, whilst the addition of HMPT promoted the formation of both oxirane and 1,4-diketone (see entry 1 of Table 1). Since phosphine oxides apparently also promote oxirane formation, we tentatively propose a common intermediate (I), from which the 1,4-diketone would be produced by migration of the 2-oxoalkyl group,<sup>8</sup> and an

oxirane by direct elimination of tributyltin bromide. A reaction path involving transformation of the oxiranes (4) to 1,4-diketones (3) was excluded by the fact that no consumption of (4aa) was observed in the reaction with equimolar amounts of Bu<sub>3</sub>SnBr and HMPT even at 70 °C for 4 h. A S<sub>N</sub>2 type reaction of tin enolates (1) to the halide moiety of halogeno ketones (2), of course, cannot be ruled out for the formation of 1,4-diketones at this stage.

In conclusion we can say that phosphine oxides co-ordinate to tin enolates to effect 1,4-diketone formation under mild conditions *via* a non-radical mechanism, and that this is a general and convenient synthesis of a variety of 1,4-diketones.

### Experimental

The reaction of acetyltributylstannane (1a) and  $\alpha$ -bromoacetophenone (2a) is representative. A mixture of (1a) (3.6 mmol) and HMPT (5.4 mmol) in dry benzene (2 ml) was stirred for 10 min under nitrogen. To this solution was slowly added a halogeno ketone (2a) (3 mmol). After 1 min, an exothermic reaction occurred and almost all of (2a) was consumed during 15 min (monitored by GLC). After the mixture had been stirred for 1 h at ambient temperature, volatiles were removed under reduced pressure, ether (100 ml) and aqueous NH<sub>4</sub>F (15%; 40 ml) were added and the resulting Bu<sub>3</sub>SnF was filtered off. The filtrate was washed with water (50 ml  $\times$  2), dried (Mg<sub>2</sub>SO<sub>4</sub>), and evaporated. The residue was flash-chromatographed (SiO<sub>2</sub>) and oxirane (4aa) (eluted by benzene-hexane, 1:3) and 1,4-diketone (3aa) (eluted by benzene-hexane, 1:1) were isolated. The oxirane (4aa),<sup>4</sup> b.p. 100 °C/5 mmHg;  $\nu_{\max}$  1 670 cm<sup>-1</sup> (C=O);  $\delta_{\text{H}}$ (CDCl<sub>3</sub>) 2.30 (3 H, s), 2.85–3.38 (4 H, m), and 7.48 (5 H, s);  $m/z$  176 ( $M^+$ ). The 1,4-diketone (3aa), b.p. 137 °C/1 mmHg;  $\nu_{\max}$  1 720 and 1 690 cm<sup>-1</sup> (C=O);  $\delta_{\text{H}}$ (CDCl<sub>3</sub>) 2.26 (3 H, s), 2.95 (2 H, t, *J* 6.24 Hz), 3.28 (2 H, t, *J* 6.24 Hz), 7.43–7.70 (3 H, m), and 7.93–8.10 (2 H, m);  $\delta_{\text{C}}$ (CDCl<sub>3</sub>) 206.71, 198.05, 136.43, 132.80, 128.29, 127.74, 36.88, 32.28, and 29.81;  $m/z$  176 ( $M^+$ ).

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