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Synthesis of 1,4-Diketones: Unusual Coupling of Tin Enolates with α-Chloro Ketones Catalyzed by Zinc Halides

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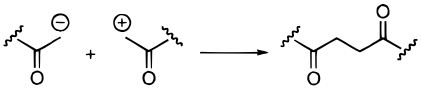
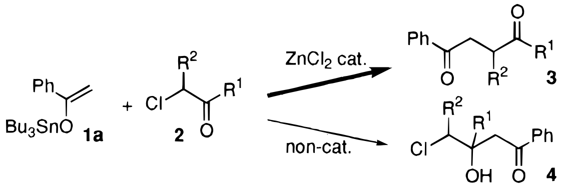
1,4-Diketones are widely used as synthetic building blocks for further elaboration into furans, cyclopentenones, or pyrroles.[1] One of the most versatile processes to 1,4-diketones is the conjugate acylation of an enone, and a variety of acyl anion equivalents have been developed.[2] Considering the applicability, a linkage of two carbonylmethyl units could be a powerful synthetic method for the synthesis of various types of 1,4-diketones. Although a number of homo-coupling reactions of carbonylmethyl radicals,[3] metal enolates,[4] or α-halocarbonyls[5] were reported, the cross-coupling of carbonylmethyl units remains a challenging problem.[6] The most straightforward process into unsymmetric 1,4-diketones is the coupling between the carbonylmethyl anion and carbonylmethyl cation (eq 1). Thus, many groups have developed different types of carbonylmethyl cation equivalents masked at the carbonyl moiety for the preparation of 1,4-diketones.[7]



(1)

The direct use of α-halocarbonyl compounds as the carbonylmethyl cation equivalent has been avoided[7h] owing to their multiple reactivity[8] such as carbonyl addition or α-proton abstraction besides the substitution at the halide carbon.[9] α-Halocarbonyls could be the most practical substrates if their reaction manner would be controlled selectively, since a variety of them are available and their preparation methods are well-known.[8] We have already attained partial success in this work for the synthesis of 1,4-diketones by the coupling of α-bromo ketones with highly coordinated tin enolates.[10,11] In the highly coordinated tin system, a direct nucleophilic substitution at the bromide moiety occurs selectively.[10b] This system, however, entails serious defects and limitations; (i) it requires more than an equimolar amount of additives as ligands to tin and (ii) it was not applicable to the coupling with α-chloro ketones at all.

Scheme 1



Herein, we report a novel reaction course for the catalytic synthesis of 1,4-diketones from tin enolates **1** and α-chloro ketones **2**. The carbonyl addition of tin enolate and the subsequent rearrangement proceed via zinc halide catalysis, and no direct substitution occurs. This new system greatly expands the scope for the synthesis of unsymmetric 1,4-diketones owing to the direct use of α-chlorinated ketones.[12]

Initially, we attempted the coupling of the tin enolate **1a** with three different types of α-chloro ketones **2a**−**c** as shown in Scheme 1 and Table 1. Under uncatalyzed conditions, only aldol-type reactions were observed, affording the functionalyzed chlorohydrin derivatives **4a**−**c** via carbonyl addition (Table 1, entries 1, 3, and 5) without any 1,4-diketones **3**.[13] Tin enolates inherently attack to the carbonyl carbon selectively rather than the halide carbon.[13−15] Gratifyingly, a dramatic change in the reaction course was achieved by the addition of a catalytic amount of $ZnCl_2$, affording the 1,4-diketones **3** exclusively (Table 1, entries 2, 4, and 6).

In the course of our investigation of other metal halides as catalysts, $MgCl_2$, LiCl, $CuCl_2$, or $AlCl_3$ failed in the

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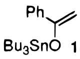
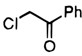
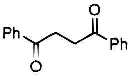
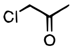
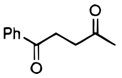
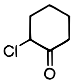
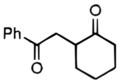
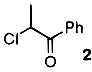
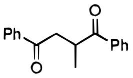
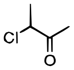
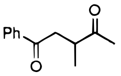
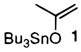
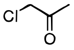
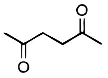
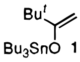
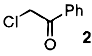
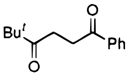
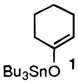
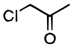
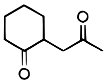
Table 1. Selective Reaction of Tin Enolate 1a with α-Chloro Ketone 2 with or without $ZnCl_2$ Catalyst (Scheme 1)[a]

entry	**2**	R^1	R^2	catalyst	time/h	yield/%	ratio of **3**/**4**
1	**2a**	Ph	H	none	6	>99	<1:>99 (**3aa**/**4a**)
2				$ZnCl_2$	2	>99	>99:<1
3	**2b**	Me	H	none	24	62	<1:>99 (**3ab**/**4b**)
4				$ZnCl_2$	2	64	>99:<1
5	**2c**	$-(CH_2)_4-$		none	24	>99	<1:>99 (**3ac**/**4c**[b])
6				$ZnCl_2$	6	82	>99:<1

[a] Tin enolate **1** (2.0 mmol) and α-chloro ketone **2** (1.0 mmol) were employed in THF (1 mL) at 40 °C. $ZnCl_2$ (0.1 mmol) was added in entries 2, 4, and 6. [b] Diastereomer ratio (60:40); ref 15.

Table 2. Synthesis of 1,4-Diketone 3 in the $ZnCl_2$-Catalyzed Reaction of Tin Enolate 1 with α-Chloro Ketone 2[a]

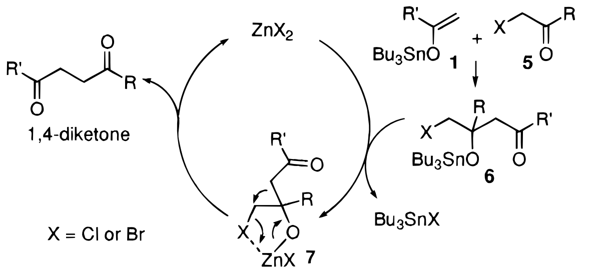
entry	tin enolate	chloro ketone	product	time/ h	yield/ %
1 2	 1a	 2a	 3aa	2 2	>99 72[b]
3 4	1a	 2b	 3ab	2 24	64 84[c]
5 6	1a	 2c	 3ac	6 2	82 75[b]
7	1a	 2d	 3ad	44	74
8	1a	 2e	 3ae	28	90
9 10	 1b	 2b	 3bb	24 8	60 75[b]
11	 1c	 2a	 3ca	3	74
12	 1d	 2b	 3db	6	47

[a] All reactions were carried out in THF (1 mL) using tin enolate **1** (2.0 mmol), chloro ketone **2** (1.0 mmol), and $ZnCl_2$ (0.1 mmol) at 40 °C. [b] $ZnBr_2$ was used instead of $ZnCl_2$. [c] The reaction was carried out at 60 °C.

effective synthesis of the 1,4-diketone, affording a complex mixture that included the substituted furan via carbonyl addition followed by cyclization[14,16] and low yields of **3a** (17, 10, 16, 40%) in the reaction of **1a** with **2a** under the same conditions. These results illustrated the effectiveness of $ZnCl_2$ for the "unusual" coupling.

We then explored the generality of the $ZnCl_2$-catalyzed reaction by varying tin enolates **1** and α-chloro ketones **2**. Table 2 summarizes these results. In all cases, the effective and exclusive formation of 1,4-diketones **3** was observed. Of course, the reaction of **1** with α-bromo ketone afforded **3** effectively.[17] The use of $ZnBr_2$ also catalyzed the reactions (Table 2, entries 2, 6, and 10). The high yield of **3ac** from cyclic chloro ketone **2c** was noteworthy (Table 2, entries 5 and 6) because no cyclic halo ketones gave 1,4-diketones by using the system of the highly coordinated tin enolate.[10b] Even the sterically hindered chloro ketones **2d** and **2e** reacted smoothly to give 1,4-diketones **3ad** and **3ae** in high yields, respectively (Table 2, entries 7 and 8). Various types of tin enolates **1a**−**d** were applied to the coupling reactions.[18]

Scheme 2



Interestingly, no reactions were observed in the treatment of **1a** with ethyl 2-chloroacetate or allyl chloride in the presence of $ZnCl_2$, which are typical types of reactive organic chlorides. The direct substitution reaction at a halide moiety, therefore, is unlikely to occur. The indispensable presence of a reactive carbonyl group attached to the chlorinated carbon strongly indicates the incorporation of the addition of a tin enolate to the carbonyl carbon in the first step. To investigate the reaction mechanism, the following experiment was carried out. After completion of the uncatalyzed addition of **1a** to the carbonyl group in **2a** under the conditions noted in entry 1 of Table 1, the addition of a catalytic amount of $ZnCl_2$ led to the transformation into **3aa** in high yield (92%). On the basis of this result, a plausible catalytic cycle is proposed in Scheme 2.

At first, the tin enolate **1** adds to the α-halo ketone **5** at the carbonyl carbon to form **6**. The transmetalation of tin in **6** with zinc halide gives the reactive intermediate zincate **7**, which can readily transform to the 1,4-diketone by rearrangement of the oxoalkyl group.[19] A generation of the zinc enolate that is formed by the transmetalation of **1** with zinc halide is also likely. Although we cannot provide the precise mechanism at this point, the intermediate zincate **7** certainly plays an important role in the rearrangement, which is prompted by the affinity of zinc with halogen in **7**.[20]

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Supporting Information Available: Experimental procedures and characterization data for all new compounds (6 pages).

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(17) The 1,4-diketone **3aa** was obtained from **1a** and 2-bromoacetophenone catalyzed by $ZnBr_2$ in 78% yield at 40 °C for 2 h.

(18) Organotin enolates exist as equilibrium mixtures of keto and/or enol forms; **1b** and **1d** exclusively exist in keto and enol forms, respectively, and **1a** and **1c** is a mixture of both forms. Pereyre, M; Bellegarde, B; Mendelsohn, J; Valade, J. *J. Organomet. Chem.* **1968**, *11*, 97−110.

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