The First Michael Addition of Metal Ketone Enolates to α,*β*-Unsaturated Esters under Catalytic Conditions: Tin Enolate with a Catalytic Amount of Tetrabutylammonium Bromide

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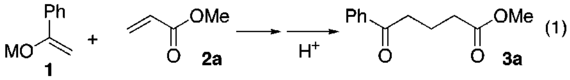
The Michael addition is an important reaction in organic syntheses,[1] in which, classically, enolate anions derived from active methylene or methine compounds are used as nucleophiles under basic conditions. In modern synthetic methodology, the metal enolates have been elegantly utilized under nearly neutral conditions.[2,3] However, the Michael addition of metal ketone enolates to α,*β*-unsaturated esters without equimolar additives has not been reported, although ester enolates are readily used for Michael donors toward α,*β*-unsaturated esters under catalytic or thermal conditions.[4,5] We, therefore, tested the reaction of methyl acrylate **2a** with metal enolates **1** (M = Li, Si, or Sn), and the results are shown in eq 1 (Scheme 1).

The lithium enolate is considered to be a typical metal enolate, and no formation of the desired Michael adduct **3a** was detected at all. This result can be explained by the thermodynamics of this reaction course. The initial product before protonolysis is **4**, which includes the metal ester enolate moiety. A metal ester enolate is generally more labile than a metal ketone enolate if the two metals are the same. Thus, a reaction of the type as shown in eq 1 would be thermodynamically disfavored in using any metals.[6,7] When silyl enolate was used, $TiCl_4$ was effectively utilized as an equimolar accelerator (Mukaiyama-type Michael addition).[8] The new Ti−O bond formation contributes to the stabilization of the product system.[9] However, the catalytic use of $TiCl_4$ resulted in low yield. The catalytic fluoride anion (Bu_4NF or CsF), which coordinates to the silicon center, also gave poor yields, although the equimolar addition accelerates the reaction.[10] To design a catalytic or thermal system in the reaction of ketone enolates with α,*β*-unsaturated esters, a number of groups have developed various indirect approaches using ortho esters,[11] thioesters,[12] a cationic species[13] or trifluoromethyl-substituted enoates[14] as unsaturated ester equivalents and *β*-lithiated enamines[15] as ketone enolate equivalents in place of the direct use of ketone enolates and α,*β*-unsaturated esters. Of course, a tin enolate also gave no products when no additive was used. Unexpectedly, we found that the tin enolate provided the Michael adduct **3a** quantitatively under the conditions in the presence of a catalytic amount of Bu_4NBr. In this paper, we report the first example of this type of reaction, which is performed using tin enolate with a catalyst under neutral conditions, and provide the rationale of this unexpected reaction course.

Scheme 1. Addition of Ketone Enolate to α,*β*-Unsaturated Ester[a]



M = Li	0%[b]
$SiMe_3$ ($TiCl_4$, 1.0 equiv)	81%[c]
$SiMe_3$ ($TiCl_4$, 0.1 equiv)	<10%[d]
$SiMe_3$ (Bu_4NF, 0.1 equiv)	<20%[e]
$SiMe_3$ (CsF, 0.1 equiv)	<5%[f]
$SnBu_3$	0%[g]
$SnBu_3$ (Bu_4NBr, 0.1 equiv)	**>99%[g]**

[a] Metal enolate **1** (3.0 equiv), methyl acrylate **2a** (1.0 equiv). [b] −78 °C, 48 h. [c] −78 °C, 15 min. [d] Less than 10% yield under any conditions of (−78 °C, 15 min), (−78 °C, 2 h), (25 °C, 6 h), or (40 °C, 12 h). [e] Less than 20% yield under any conditions of (−78 °C, 15 min), (0 °C, 0.5 h), (25 °C, 6 h), or (63 °C, 6 h). [f] 63 °C, 6 h. [g] 63 °C, 12 h.

In view of the interest in the generality of this method, we explored several sets of representative enolates and unsaturated carbonyls as summarized in Table 1. In almost all cases, the effective formation of *δ*-dicarbonyl compounds **3** was observed. 2-Thienyl-substituted enolate **1b** gave the keto ester **3b** in 91% yield. The enolates substituted at the reaction site showed similar reactivities (entries 3 and 4). The reaction of cyclic enolate **1c** proceeded even at 25 °C because of its high reactivity while the tin enolate **1e** afforded a low yield.[16,17] This reaction system was also applied to α,*β*-unsaturated amide **2c**. The reaction with unsaturated ketones **2d** and **2e** afforded 1,4-adducts **3g** and **3h** exclusively in high yields without 1,2-adducts.[3,18]

It is indicated that the reaction of tin enolates would be thermodynamically favored, since this system is carried out

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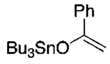
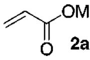
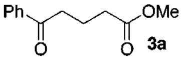
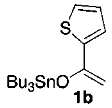
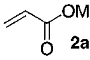
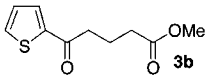
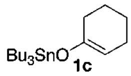
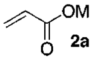
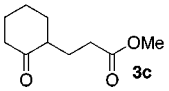
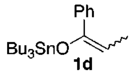
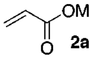
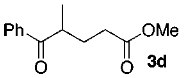
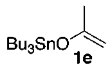
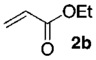
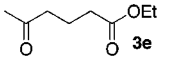
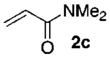
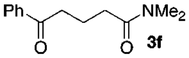
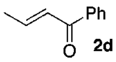
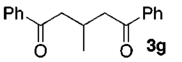
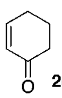
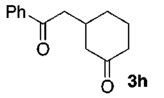
10.1021/jo990062b CCC: $18.00

Table 1. Michael Addition of Tin Enolate 1 to α,β-Unsaturated Carbonyls 2 Catalyzed by Bu_4NBr[a]

entry	enolate	unsaturated carbonyl	time/h	product	yield/%
1	 1a	 2a	12	 3a	>99
2	 1b	 2b	12	 3b	91
3	 1c	 2a	14	 3c	>99[b]
4	 1d	 2a	12	 3d	86
5	 1e	 2b	19	 3e	16
6	1a	 2c	12	 3f	62
7	1a	 2d	12	 3g	93
8	1a	 2e	12	 3h	>99

[a] The reactions were performed using tin enolate **1** (3.0 mmol), unsaturated carbonyl **2** (1.0 mmol), and Bu_4NBr (0.1 mmol) in refluxing THF (10 mL). [b] 25 °C.

Scheme 2. Plausible Reaction Mechanism

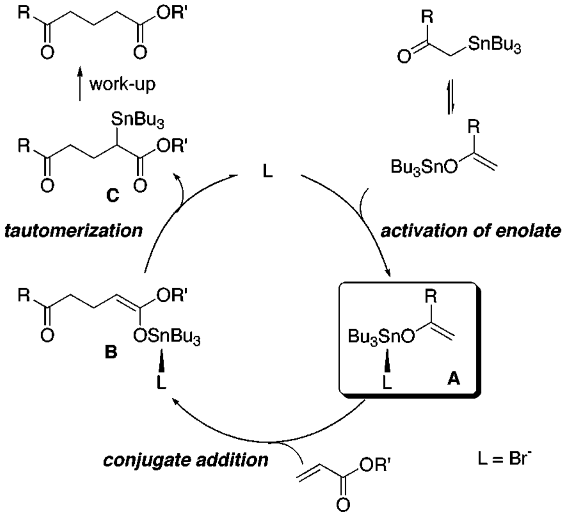
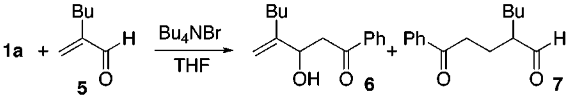
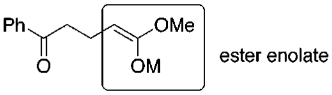


Table 2. Chemoselective Control of Tin Enolate 1a with Enal 5[a]



entry	mmol (Bu_4NBr)	T/°C	time/h	yield/%	ratio **6**:**7**
1	0	25	6	86	>99:<1
2	0.1	63	3	60	37:63
3	2.0	25	17	54	10:90

[a] The reactions were performed using tin enolate **1a** (3.0 mmol), enal **5** (1.0 mmol), and additive in THF (10 mL).



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under catalytic conditions. We propose a plausible reaction mechanism as shown in Scheme 2. The tautomerization of tin ester enolate **B** corresponding to **4** into stable keto-type tin compound **C** contributes to the stabilization of the product system. It has been reported that α-stannyl esters are far more stable than tin ester enolates and the tautomeric equilibrium lies well to the stannyl ester species.[16,19] Other metal species such as Li or Si do not show the tautomerization. Because the reaction without Bu_4NBr did not proceed at all, the bromide-anion-coordinated tin enolate **A** is strongly indicated to play an important role in kinetics.[20,21] Our previous paper discloses that the high coordination of tin enolates increases the polarization at the reaction site, which reflects the nucleophilicity.[20a] The activation energy of the Michael reaction is thus lowered by the high coordination.[22] A C-stannylated species such as **C** is reluctant to be coordinated in comparison with the corresponding O-stannyl species such as **B**.[23] The ligand L can be smoothly regenerated at the tautomerization step. These features accomplish the presented Michael addition in a catalytic system.

The conjugate addition to α,β-unsaturated aldehyde is a more challenging problem due to its high reactivity at the formyl group.[24] Indeed, the reaction of **1a** with the enal **5** gave the 1,2-adduct **6** exclusively (Table 2, entry 1). The addition of a catalytic amount of Bu_4NBr dramatically changed the chemoselectivity into 1,4-addition, giving the δ-keto aldehyde **7** (**6**:**7** = 37:63). The predominant formation of **7** (**6**:**7** = 10:90) by larger amount of Bu_4NBr apparently indicates that the change in chemoselectivity resulted from the coordination of a bromide anion.[25]

Investigation of the scope and limitation of this catalyzed system and its detailed reaction mechanism is in progress.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds.

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[19] For the organotin ester enolates, the equilibrium between O-stannylated and C-stannylated forms generally lies to the C-stannylated species above 0 °C. Shimada, E.; Inomata, K.; Mukaiyama, T. *Chem. Lett.* **1974**, 689–690.

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[25] The coordination by bromide anion suppresses the carbonyl addition of the tin enolate (ref 20a).