Remarkable Enhancement of Nucleophilicity of Tin Enolates toward Nitro- or Cyanoalkenes by Tetrabutylammonium Halides

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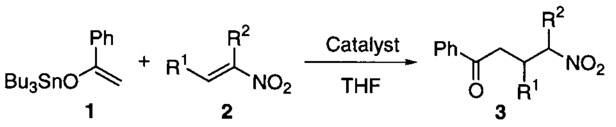
The reaction of tin enolates with nitroalkenes was effectively catalyzed by tetrabutylammonium bromide (Bu_4NBr) to give γ-nitroketones. When the substituted tin enolates at the β-carbon in the olefinic moiety were used, the diastereoselective addition proceeded through the acyclic transition state. Tetrabutylammonium chloride (Bu_4NCl) strongly accelerated the reaction with the cyanoalkene to give the γ-cyanoketone.

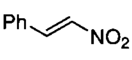
Organotin compounds have been used as versatile reagents for organic syntheses.[1] They usually require an activator to accomplish the reactions because of their moderate reactivity. Therefore, the activation methodology of the reaction using tin reagents is significantly important and could lead to selective reaction courses. The organotin(IV) has ability to accept ligands to form a highly coordinated species owing to their vacant d-orbitals.[2] Our recent research disclosed that some appropriate ligands form five-coordinated organotin(IV) enolates, which have totally different reactivity from that of noncoordinated enolates.[3] In particular, we have previously reported the Michael addition of organotin(IV) enolates to α,β-unsaturated esters, ketones, and amides in the presence of a catalytic amount of tetrabutylammonium bromide which donates the bromide anion to the tin center.[4] In this reaction course, five-coordinated tin enolate, which is catalytically generated, is a key species. We, then have been interested in other Michael acceptors for the reaction using tin enolates. In this paper, the dramatic enhancement of nucleophilicity of tin enolate by tetrabutylammonium halides toward nitro- and cyanoalkenes to afford γ-nitro- and cyanoketones, respectively, is reported.

Table 1. Michael addition of tin enolate to nitroalkene[a]

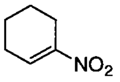


Entry	2	Catalyst	T/°C	t/h	Yield/%
1	**2a**	none	rt	12	66 (**3a**)
2	**2a**	none	-45	4	0 (**3a**)
3	**2a**	Bu_4NBr	-45	4	94 (**3a**)
4	**2a**	Bu_4NBr	rt	12	60 (**3a**)
5	**2a**	Bu_4NBr	-50	4	82 (**3a**)
6	**2b**	Bu_4NBr	-40	4	71 (**3b**)[b]

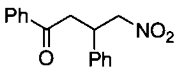
[a] All reactions were carried out in THF using tin enolate **1** (3 equiv), **2** (1 equiv), and catalyst (0.1 equiv). [b] *cis* : *trans* = 83:17.



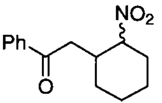
2a



2b



3a

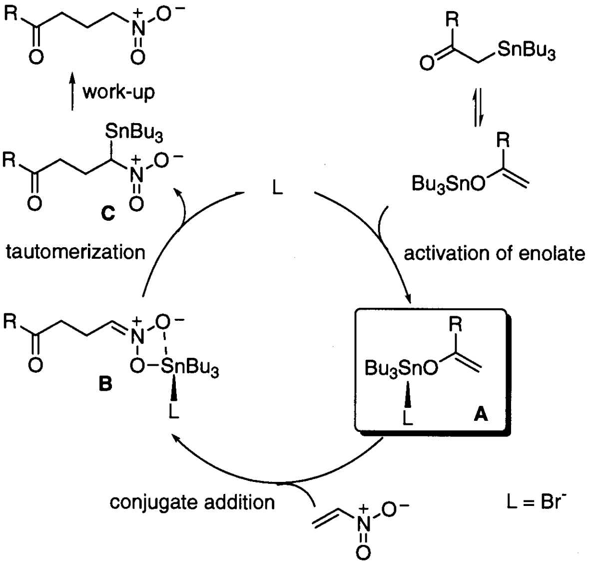


3b

The reaction of tin enolate **1** with β-nitrostylene **2a** at room temperature gave the γ-nitroketone **3a** in 66% yield although accompanied with unidentified complicated products (Table 1, entry 1).[5] To avoid the formation of side products, the reaction was performed at low temperature (–45 °C), but gave no products at all (entry 2). The loading of a catalytic amount of Bu_4NBr significantly accelerated the Michael addition to give **3a** in 94% yield even at –45 °C (entry 3).[6] Lower yield was observed in the reaction with catalytic Bu_4NBr at room temperature owing to the complicated side products which probably came from the over-reactions (entry 4). The conditions at low temperature with a catalytic amount of Bu_4NBr was also applied to the cyclic nitroalkene **2b** to afford 71% yield of **3b** (entry 6).

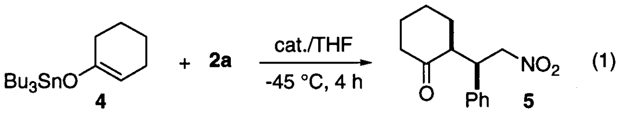
A plausible reaction mechanism is shown in Scheme 1. The high coordination by the bromide anion causes increase of nucleophilicity in the tin enolate.[3,4] The generated active species **A** attacks the β-carbon of nitro-substituted olefin to form **B**. The tautomeric isomerization to the stable species **C** takes place with releasing the ligand L as already reported in the reaction with unsaturated esters.[4] In this step, the ligand L is readily dissociated from **C** and coordinates to the tin enolate because the tendency of coordination clearly depends on the Lewis acidity of the tin center; oxo-substituted stannane **A** has higher Lewis acidity than tetra *C*-substituted stannane **C**.[3a,c]

The substituted tin enolates at the β-carbon in the olefinic moiety could provide the diastereoselective reaction course



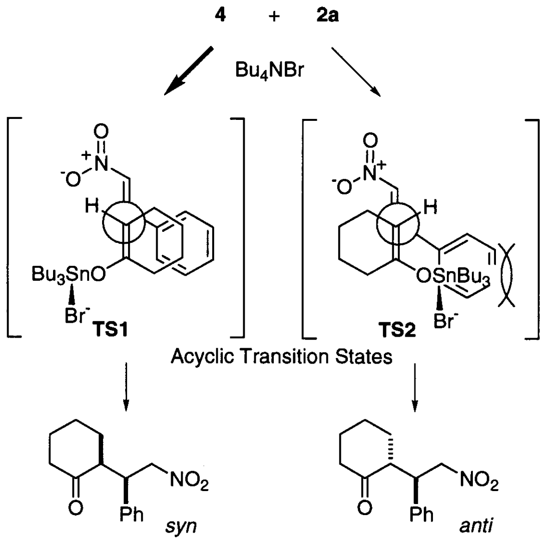
Scheme 1. Plausible reaction mechanism.

with the substituted nitroalkene. In fact, the reaction of **4** with **2a** gave the product **5** quantitatively with 86/14 diastereomeric ratio in the presence of Bu_4NBr (eq 1).[7] On the contrary, non-catalyzed reaction gave lower yield and selectivity.[8]



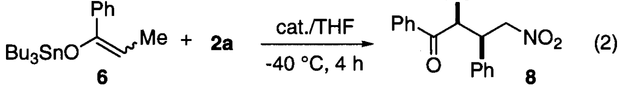
Bu_4NBr	>99%	*syn* : *anti* = 86:14
none	22%	*syn* : *anti* = 63:37

The high selectivity using Bu_4NBr can be explained by Scheme 2, although the exact mechanism is unclear at this stage.[9] Since the highly coordinated trialkyltin is not likely to accept another ligand,[3a] the acyclic transition states are reasonably assumed for the reaction between **4** and **2a** in the presence of Bu_4NBr. The transition state **TS1**, which leads to *syn*-product, is preferred to **TS2** because of the steric hindrance between phenyl and the bulky highly coordinated tin in **TS2**.



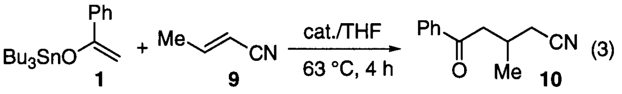
Scheme 2. Transition states in the reaction of **4** with **2a**.

The acyclic tin enolate **6** showed high yield and selectivity in the presence of Bu_4NBr-catalyst (eq 2).[10] This result probably means that the geometry of **6** in the transition state is *E*-form in this reaction.



Bu_4NBr	>99%	*syn* : *anti* = 84:16
none	39%	*syn* : *anti* = 74:26

Finally, we examined cyanoalkene as the Michael acceptor. The non-catalyzed reaction of **1** with **9** at room temperature or higher temperature (63 °C) gave no product, and the starting materials were recovered (eq 3). The addition of a catalytic amount of Bu_4NBr gave only 27% of the product **10** even at 63 °C. The yield was improved by use of Bu_4NCl instead of Bu_4NBr to give **10** in 44%. We have reported that the coordination ability of chloride to tin enolates is too high to be utilized for the reaction probably because of their decomposition.[3b] However, the result in eq 3 suggests the potential of the chloride anion as an accelerator of tin enolates in the case of catalytic use.



none	0%
Bu_4NBr	27%
Bu_4NCl	44%

We are currently developing this methodology for other substrates and reagents.

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References and Notes

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4 M. Yasuda, N. Ohigashi, I. Shibata, and A. Baba, *J. Org. Chem.*, **64**, 2180 (1999).

5 Organotin enolates exist as equilibrium mixtures of keto- and/or enol-forms, the ratio of which largely depends on their substituents and conditions. M. Pereyre, B. Bellegarde, J. Mendelsohn, and J. Valade, *J. Organometal. Chem.*, **11**, 97 (1968). Since higher reactivity is generally shown by enol-types than keto-ones (K. Kobayashi, M. Kawanisi, T. Hitomi, and S. Kozima, *Chem. Lett.*, **1983**, 851), all structures of tin enolates in this paper are drawn in enol-forms.

6 Typical experimental procedure for the synthesis of **3a**: To a mixture of tin enolate **1** (3.0 mmol) and Bu_4NBr (0.1 mmol) in dry THF (5 mL) at 45 °C was added β-nitrostylene **2a** (1.0 mmol) under nitrogen. The reaction mixture was stirred for 4 h at the same temperature. Diethyl ether (30 mL) and aqueous NH_4F (15%; 15 mL) were then added to the solution and the homogeneous mixture was vigorously stirred for 15 min and the insoluble solids were filtered off. The filtrates were extracted with diethyl ether and the organic layer was dried over $MgSO_4$ and evaporated. Column chromatography (hexane/Et_2O, 5/2) of the resultant residue on silica gel gave **3a** as a pure form.

7 The spectral data of **5** were reported. E. Juaristi, A. K. Bech, J. Hansen, T. Matt, T. Mukhopadhyay, M. Simson, and D. Seebach, *Synthesis*, **1993**, 1271.

8 In this case, the Michael adduct was obtained although the yield was very low. The tin enolate **4** has higher reactivity than **1** because the enol ratio in tautomerism is highly favorable (ref 5).

9 Either an acyclic or a cyclic transition state is proposed for the reaction of metal enolates with unsaturated carbonyls. a) C. H. Heathcock, M. H. Norman, and D. E. Uehling, *J. Am. Chem. Soc.*, **107**, 2797 (1985). b) D. A. Oare and C. H. Heathcock, *J. Org. Chem.*, **55**, 157 (1990).

10 The spectral data of **8** were reported. F. Felluga, P. Nitti, G. Pitacco, and E. Valentin, *Tetrahedron*, **45**, 2099 (1989).