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Synthetic Utility of Stannyl Enolates as Radical Alkylating Agents[1]

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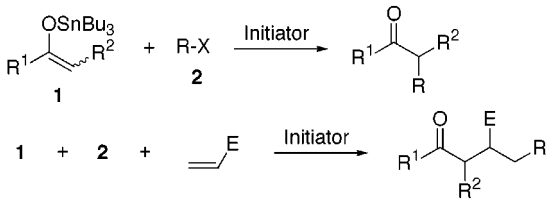
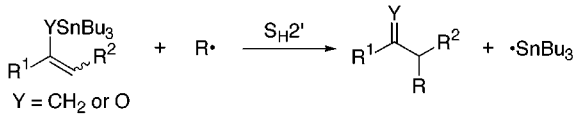
ABSTRACT



The radical-initiated β-ketoalkylation of haloalkanes with tributylstannyl enolates is described. Stannyl enolates derived from aromatic ketones are reactive toward the homolytic β-ketoalkylation of simple haloalkanes as well as those activated by an electron-withdrawing group. The reactivity of stannyl enolates as radical alkylating agents can be utilized for an efficient three-component coupling reaction among stannyl enolates, haloalkanes, and electron-deficient alkenes.

It is well recognized that allylstannanes serve as radical allylating agents (Scheme 1, Y = CH_2).[1,2] Acyclic stereocontrol of the homolytic allylation has been the focus of intensive investigation in recent years.[4] Stannyl enolates, oxygen analogues of allylstannanes, are also known to work as radical alkylating agents (Scheme 1, Y = O).[5,6] Russell and Herold have reported the photostimulated homolytic substitution (S_H2') of stannyl enolates with polyhalomethanes.[5] Toru et al. have shown that the photostimulated reaction of acetonyltributylstannane with α-phenylseleno- and α-halocarbonyl compounds gives 1,4-dicarbonyl compounds.[6] This reaction has been also proposed to proceed via a radical chain mechanism involving the S_H2' reaction of stannyl enolate arising from the α-stannyl ketone by metallotropic isomerization.[7] Despite these reports, the synthetic utility of stannyl enolates as radical alkylating agents remains largely unexplored in contrast to that of allylstannanes. Here we disclose that some stannyl enolates work as good radical alkylating agents in the Et_3B- or AIBN-initiated reaction of various radical precursors, and the reactivity of stannyl enolates can be successfully applied to a radical-based three-component coupling reaction.

Scheme 1



Initially, we examined homolytic β-ketoalkylation of haloalkanes with tributylstannyl enolate **1a** derived from

(1) Free Radical Chemistry. 37. For part 36, see: Miura, K.; Saito, H.; Itoh, D.; Matsuda, T.; Fujisawa, N.; Wang, D.; Hosomi, A. *J. Org. Chem.* **2001**, *66*, 3348.

(2) Reviews: (a) Davies, A. G. *Organotin Chemistry*; VCH: Weinheim, 1997. (b) Curran, D. P. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, p 715. (c) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon−Carbon Bonds*; Pergamon Press: Oxford, 1986.

(3) (a) Kosugi, M.; Kurino, K.; Takayama, K.; Migita, T. *J. Organomet. Chem.* **1973**, *56*, C11. (b) Grignon, J.; Pereyre, M. *J. Organomet. Chem.* **1973**, *61*, C33. (c) Keck, G. E.; Yates, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 5829.

(4) Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2562.

(5) Russell, G. A.; Herold, L. L. *J. Org. Chem.* **1985**, *50*, 1037.

(6) Watanabe, Y.; Yoneda, T.; Ueno, Y.; Toru, T. *Tetrahedron Lett.* **1990**, *31*, 6669.

(7) Kobayashi, K.; Kawanisi, M.; Hitomi, T.; Kozima, S. *Chem. Lett.* **1984**, 497.

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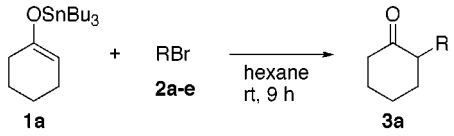
cyclohexanone.[8] In the presence of AIBN (5 mol %), simple haloalkanes such as *i*-PrI and *t*-BuI did not react with **1a** (4 equiv) in benzene at 80 °C. In contrast, methyl bromoacetate (**2a**) underwent alkylation with **1a** to give γ-ketoester **3aa** in 69% yield. The use of Et_3B (10 mol %) as initiator in hexane at room temperature improved the yield to 92%.[9] As shown in Table 1 (method A), 2 equiv of **1a** was enough

Table 1. Reaction of Bromoalkanes with Stannyl Enolate **1a**[a]



haloalkane			yield (%) by methods A−D			
R		product	A	B	C	D
MeO_2CCH_2	**2a**	**3aa**	90, 71[b]	14	<1	0
$NCCH_2$	**2b**	**3ab**	98, 86[b]	96	3	0
$EtO_2CCH(Me)$	**2c**	**3ac**	15	0	0	
NCCH(Me)	**2d**	**3ad**	26	<1	0	
$(MeO_2C)_2CH$	**2e**	**3ae**	89, 95[b]	11	3	0

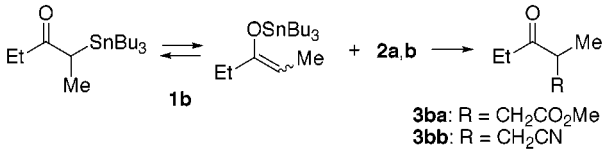
[a] Method A: **1a** (1.00 mmol), **2** (0.50 mmol), Et_3B (0.05 mmol), hexane (2.5 mL), dry air (10 mL), rt, 9 h. Method B: method A without Et_3B and dry air. Method C: method A with galvinoxyl (0.05 mmol). Method D: method C without Et_3B and dry air. [b] **1a** (0.60 mmol).

to achieve high efficiency in the Et_3B-initiated reaction of **2a**. Under the same conditions, bromoacetonitrile (**2b**) and dimethyl bromomalonate (**2e**) also showed high reactivity to **1a**, while ethyl 2-bromopropanoate (**2c**) and 2-bromopropanenitrile (**2d**) were much less reactive.

It has been reported that haloalkanes are spontaneously β-ketoalkylated with stannyl enolates under solvent-free conditions at elevated temperatures (80−140 °C).[10] Control experiments without Et_3B (method B in Table 1), however, demonstrated that the spontaneous reaction of **2** with **1a** was rather slow except for the case with **2b**. The addition of galvinoxyl, a radical scavenger, markedly retarded both the Et_3B-initiated and spontaneous alkylation of **2** (methods C and D). These observations support the fact that Et_3B serves as a radical initiator to promote the alkylation, and the spontaneous alkylation as well passes through a radical chain process. The initiation step in the absence of a radical initiator may be caused by electron transfer from **1a** to **2**.[11]

Stannyl enolate **1b** derived from 3-pentanone exists as a tautomeric mixture of keto and enol forms (keto:*E*-enol:*Z*-enol = 25:60:15 in C_6D_6); however, the β-ketoalkylation of **2a**,**b** with **1b** efficiently proceeded by method A (Scheme 2). The AIBN-initiated reaction with **1b** (2 equiv) in benzene at 80 °C (method E) achieved better yields of **3ba** and **3bb**. These products were formed even in the absence of AIBN

Scheme 2



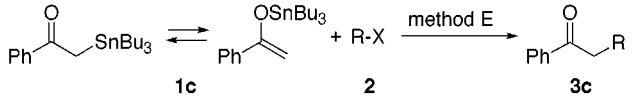
Method A: **3ba**, 80%; **3bb**, 72%
Method E: **3ba**, 88%; **3bb**, 90%

Method E: **1** (1.00 mmol), **2** (0.50 mmol), AIBN (0.025 mmol), PhH, 80 °C, 4 h

(**3ba**, 55%; **3bb**, 94%). Similar to the case with **1a**, the spontaneous alkylation was suppressed in the presence of galvinoxyl (**3ba**, 8%; **3bb**, 16%).

We next investigated the reactivities of stannyl enolates derived from aromatic ketones. Acetophenone stannyl enolate **1c** favors the keto form (keto:enol = 74:26 in C_6D_6).[12] Nonetheless, it was found that **1c** has high reactivity toward the β-ketoalkylation of various radical precursors in the AIBN-initiated system (Table 2).[13] Activated haloalkanes

Table 2. Reaction of Various Radical Precursors with Stannyl Enolate **1c**[a]



	radical precursor				
entry	R−X		product	yield (%)	
1	MeO_2CCH_2−Br	**2a**	**3ca**	86, 94[b]	
2	$NCCH_2$−Br	**2b**	**3cb**	89	
3	$EtO_2CCH(Me)$−Br	**2c**	**3cc**	95	
4	NCCH(Me)-Br	**2d**	**3cd**	quant, 22[c]	
5	$(MeO_2C)_2CH$−Br	**2e**	**3ce**	86, quant[b]	
6	$PhCOCH_2$−Br	**2f**	**3cf**	85, 52[c]	
7	Et-I	**2g**	**3cg**	33, 79[d]	
8	*i*-Pr−I	**2h**	**3ch**	61, 97[d]	
9	*i*-Pr−Br	**2i**	**3ch**	89[d]	
10	*t*-Bu-I	**2j**	**3cj**	65, quant[d]	
11	$AcO(CH_2)_3$−I	**2k**	**3ck**	81[d]	
12	$THPO(CH_2)_3$−I	**2l**	**3cl**	70[d]	
13	MeO_2CCH_2−SPh	**2m**	**3ca**	42	
14	MeO_2CCH_2−OC(S)OPh	**2n**	**3ca**	88	
15	*i*-Pr−OC(S)OPh	**2o**	**3ch**	54, 63[e]	

[a] Unless otherwise noted, all reactions were performed according to method E. For method E, see Scheme 2. [b] **1c** (0.60 mmol). [c] Without AIBN. [d] **1c** (2.00 mmol), AIBN (0.050 mmol). [e] AIBN (0.050 mmol).

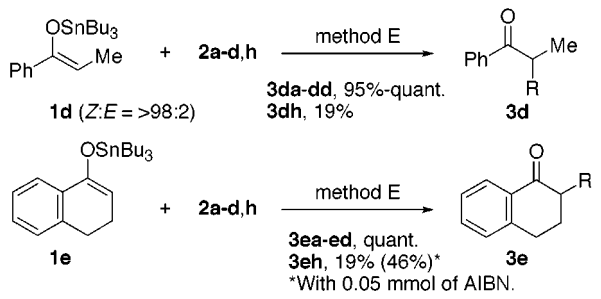
2a−**f** smoothly reacted with **1c** to give the corresponding adducts **3ca**−**cf** in high yields (entries 1−6). Under the same conditions (method E), simple haloalkanes **2g**−**j** underwent

(8) For preparation of stannyl enolates, see: Pereyre, M.; Bellegarde, B.; Mendelsohn, J.; Valade, J. *J. Organomet. Chem.* **1968**, *11*, 97.
(9) Nozaki, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 2547.
(10) Odic, Y.; Pereyre, M. *J. Organomet. Chem.* **1973**, *55*, 273.
(11) Li, X.; Chen, J. J.; Tanner, D. D. *J. Org. Chem.* **1996**, *61*, 4314.
(12) Yasuda, M.; Katoh, Y.; Shibata, I.; Baba, A.; Matsuda, H.; Sonoda, N. *J. Org. Chem.* **1994**, *59*, 4386.
(13) The Et_3B-initiated reaction in benzene at 80 °C was less effective in the alkylation with **1c**. For example, under these conditions, the alkylation of **2a** with **1c** resulted in 13% yield after 4 h.

alkylation with **1c** in moderate yields (entries 7−10). Increasing the amount of AIBN and **1c** was effective in improving the yield. Functionalized unactivated haloalkanes **2k**,**l** were also available for the present alkylation (entries 11 and 12). Instead of haloalkanes, phenylsulfide **2m** and thiocarbonates **2n**,**o**[14] could be alkylated with **1c**. In the absence of AIBN, the reactions shown in Table 2 did not proceed to a significant extent except for the alkylation of **2d** and **2f**, in which **3cd** and **3cf** were obtained in 22% and 52% yields, respectively (entries 4 and 6).

Stannyl enolates **1d** and **1e**, which exist as enol forms, exhibited high reactivity to activated haloalkanes as did **1c**, while they were less reactive to simple haloalkanes than **1c** (Scheme 3). The low reactivity is attributable to the sterically

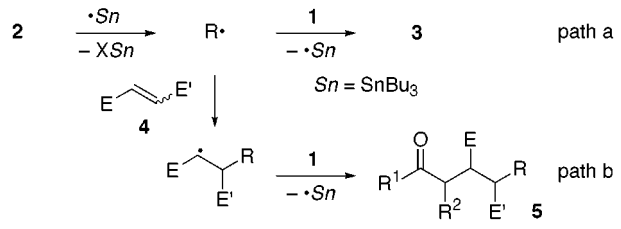
Scheme 3



crowded reaction site in the enolates, which would retard the homolytic substitution step in the chain process.

The present homolytic β-ketoalkylation would involve the following propagation step (path a in Scheme 4): a tribu-

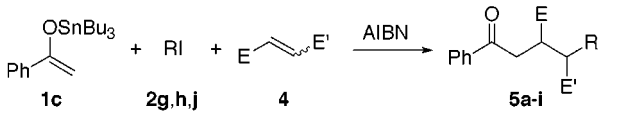
Scheme 4



tylstannyl radical abstracts an atom or a group from **2** to generate an alkyl radical (R•) and the radical reacts with **1** by the S_H2' mechanism to give **3** and regenerate the stannyl radical. The high reactivity of haloalkanes activated by an electron-withdrawing group can be rationalized by a polar effect in the latter homolytic substitution step: Electron-deficient radicals show high reactivity to electron-rich alkenes such as stannyl enolates.[2b,15] In this reaction system, the coexistence of alkene **4** able to trap the alkyl radical is expected to give the three-component coupling product **5** (path b). A similar type of radical-based coupling reaction using allylstannanes has been reported to provide a powerful synthetic tool.[16] Encouraged by the above result that stannyl enolates serve as good radical alkylating agents, we next directed our efforts to the three-component coupling reaction among stannyl enolates, haloalkanes, and alkenes. For a successful coupling, the radical intermediate R• should be more reactive to **4** than to **1**; therefore, simple iodoalkanes **2g**,**h**,**j** and electron-deficient alkenes **4a**−**d** were selected as the substrates.[17] Additionally, stannyl enolates **1c**−**e** were used in view of their high reactivities to secondary alkyl radicals conjugated with an electron-withdrawing group.[17]

The results with **1c** are shown in Table 3. As expected,

Table 3. Three-Component Coupling Reaction[a]



	iodoalkane		alkene				
entry	R		E	E′		product	yield (%)[b]
1	Et	**2g**	MeO_2C	H	**4a**	**5a**	68
2	*i*-Pr	**2h**	MeO_2C	H	**4a**	**5b**	78, 62[c]
3	*t*-Bu	**2j**	MeO_2C	H	**4a**	**5c**	73
4	Et	**2g**	NC	H	**4b**	**5d**	88
5	*i*-Pr	**2h**	NC	H	**4b**	**5e**	90
6	*t*-Bu	**2j**	NC	H	**4b**	**5f**	85
7	Et	**2g**	MeO_2C	CO_2Me	**4c**[d]	**5g**	95 (74:26)
8	*i*-Pr	**2h**	MeO_2C	CO_2Me	**4c**	**5h**	quant (81:19)
9	*t*-Bu	**2j**	MeO_2C	CO_2Me	**4c**	**5i**	85 (>99:1)
10	*i*-Pr	**2h**	MeO_2C	CO_2Me	**4d**[e]	**5h**	93 (81:19)

[a] Unless otherwise noted, all reactions were performed with **1c** (1.00 mmol), **2** (0.50 mmol), and **4** (1.00 mmol) in benzene (2.5 mL) at 80 °C for 4 h. [b] Isomeric ratios are shown in parentheses. [c] With **1c** (0.50 mmol) and **4a** (0.50 mmol). [d] Dimethyl fumarate. [e] Dimethyl maleate.

the AIBN-initiated reaction among **1c**, simple iodoalkanes, and **4** gave the desired coupling products **5a**−**i** in good to high yields. The yields are correlated with the radical-accepting ability of the alkenes except for the case with dimethyl maleate (**4d**).[18] The use of dimethyl fumarate (**4c**) led to high efficiency of the coupling reaction with moderate to high diastereoselectivity (entries 7−9). The stereoselectivity was independent of the geometry of the alkene (entries 8 and 10). Judging from the report by Giese et al.,[19] the radical intermediate generated by radical addition to **4c**,**d**

(14) Robins, M. J.; Wilson, J. S.; Hansske, F. *J. Am. Chem. Soc.* **1983**, *105*, 4059.

(15) Giese, B.; He, J.; Mehl, W. *Chem. Ber.* **1988**, *121*, 2063.

(16) (a) Mizuno, K.; Ikeda, M.; Toda, S.; Otsuji, Y. *J. Am. Chem. Soc.* **1988**, *110*, 1288. (b) Keck, G. E.; Kordik, C. P. *Tetrahedron Lett.* **1993**, *34*, 6875. (c) Sibi, M. P.; Ji, J. *J. Org. Chem.* **1996**, *61*, 6090 and references therein.

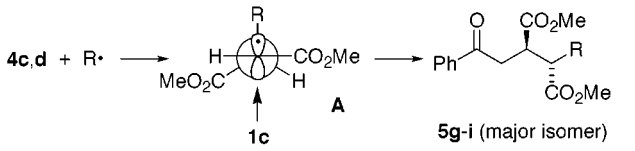
(17) Indeed, the reaction among **1c**, **2a**, and **4a** gave only **3ca**. The use of **1a** failed in the three-component coupling reaction.

(18) The relative rate constants in the addition of cyclohexyl radical to **4** are 1.0 (**4a**, standard), 3.6 (**4b**), 5.0 (**4c**), and 0.5 (**4d**). Giese, B. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 753. Thus, the reactivity of **4d** is not as high as that of other alkenes, but the present reaction with **4d** shows higher efficiency than that with **4a** or **4b**. This observation is probably due to the stannyl radical-mediated isomerization of **4d** to **4c**.

(19) Giese, B.; Damm, W.; Wetterich, F.; Zeitz, H.-G. *Tetrahedron Lett.* **1992**, *33*, 1863.

would mainly take the conformation **A** because of dipole−dipole repulsion between the two ester groups, and the subsequent reaction with **1c** would occur preferentially in the opposite side to R (Scheme 5). Therefore, the major

Scheme 5

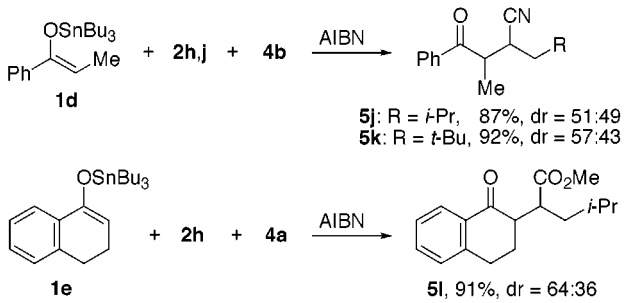


isomers can be deduced to have anti (erythro) configuration.

Stannyl enolates **1d**,**e** also underwent the three-component coupling reaction to afford **5j**−**l** in high yields but with low diastereoselectivity (Scheme 6).

In conclusion, we have demonstrated that stannyl enolates are valuable for alkylation of alkyl radicals conjugated with an electron-withdrawing group. Particularly, acetophenone stannyl enolate **1c** shows high reactivity to a variety of alkyl radicals including nucleophilic ones such as Et•, *i*-Pr•, and *t*-Bu•. In addition, we have developed a new three-component

Scheme 6



radical coupling reaction utilizing the high radical alkylating ability of stannyl enolates **1c**−**e**.

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Supporting Information Available: Experimental procedure and spectral data for stannyl enolates **1** and products **3** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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