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Participation of Organotin Lewis Acids in Radical Reactions: Manipulation of Rotamer Population in *N*-Enoyloxazolidinones

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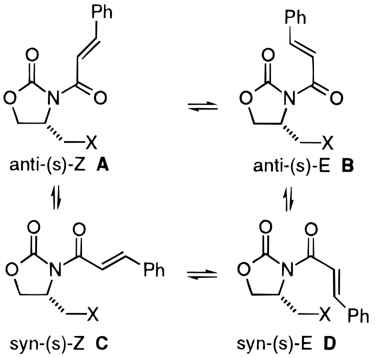
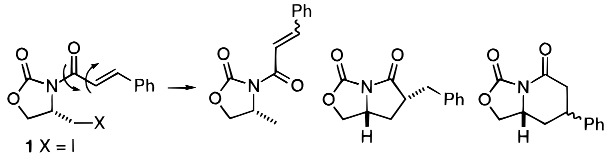
Strategies involving radical intermediates have emerged as important tools in synthetic organic chemistry.[1] Since most radical reactions proceed through early transition states, the geometries of the reactants play an important role in the regio- and stereochemical outcomes. The rotamer populations of components in radical reactions have been controlled by factors such as temperature,[2] Lewis acids,[3] dipole−dipole interactions,[4] and steric interactions.[5] In this communication we demonstrate that temperature and/or Lewis acids can control the rotamer populations of *N*-enoyloxazolidinones (**A**−**D**), leading to selective intramolecular radical cyclizations. The results show for the first time that organotin halides, ubiquitous byproducts of many radical reactions, can function as Lewis acids and alter the course of these reactions.


anti-(s)-Z **A**
anti-(s)-E **B**
syn-(s)-Z **C**
syn-(s)-E **D**

The results for reductive cyclization of **1** and **2**[6] (Scheme 1) are shown in Table 1. Reaction of **1** at room temperature using Bu$_3$SnH/AIBN gave the reduction product **3** but no cyclization (entry 1).[7] Although the reaction could be accelerated by light (sunlamp, 275 W) at room temperature, **3** was still the only product (entry 2).[8] The reaction gave similar results when tris(trimethylsilyl)silane (TTMSS) was used as the hydrogen atom donor (compare entries 2 and 3). The formation of **3** and the absence of the 5-*exo* and 6-*endo* products **4** and **5** suggest that neither conformation **C** or **D** is present to a significant extent.[9]

Scheme 1


1 X = I
2 X = Br
3
4 (5-exo)
5 (6-endo)

When a solution of Bu$_3$SnH/AIBN (syringe pump, 5 h) was added to a refluxing benzene solution of **1**, 5-*exo* cyclization product **4** was formed in good yield with high *cis* diastereoselectivity (entry 4). Thus, in keeping with the Curtin−Hammett principle, raising the temperature provided a simple technique for enhancing the equilibration rate and equilibrium population of the minor *syn* conformer **C**, leading to product **4**. The minor amount of the reduction product **3** could be eliminated entirely by decreasing the rate of Bu$_3$SnH addition (entry 5). Use of Ph$_3$SnH gave similar results (entry 6).

Surprisingly, under analogous conditions TTMSS furnished the reduction product **3** as the major product (entry 7). The unexpected dependence of the product distribution on the nature of the hydrogen atom donor[10] indicated that the organotin halide byproduct plays an important role.[11] To test this hypothesis, an organotin halide was added prior to the reaction of **1** with TTMSS (entries 8−12). Under these conditions, the 5-*exo* cyclization product **4** was again formed cleanly and with high diastereoselectivity. Control experiments showed that TTMSS and Bu$_3$SnCl do not react with each other to give Bu$_3$SnH under the reaction conditions. Either stoichiometric or substoichiometric amounts of organotin Lewis acid additives dramatically enhanced the chemoselectivity for cyclization.[12] The reactions with Bu$_3$SnH alone generate Bu$_3$SnI, which functions as a chelating Lewis acid, whereas reactions with TTMSS generate tris(trimethylsilyl) iodide, which is incapable of two-point binding. When the radical precursor was bromide **2** rather than iodide **1**, the diastereomeric excess (de) of the cyclization product dropped from >97% to 59% (compare entry 13 with 5). Addition of an equivalent of tributyltin chloride restored the de to 92% (entry 14). Thus, organotin halides can have dramatic effects on both diastereo- and chemoselectivity.

In light of the unusual reactivity of the organotin halides, we sought to examine them and a few conventional Lewis acids as additives in cyclization of **1** at room temperature (entries 15−18). Some interesting trends emerge. Strong Lewis acids, such as magnesium bromide or diethylaluminum chloride, gave only the reduction product **3**. However, when tributyltin chloride was used as the additive, a small amount of the cyclization

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(3) For selected examples, see: (a) Renaud, P.; Bourquard, T; Gerster, M; Moufid, N. *Angew. Chem., Int. Ed. Engl.* **1994,** *33,* 1601. (b) Yamamoto, Y.; Onuki, S.; Yumoto, M.; Asao, N. *J. Am. Chem. Soc.* **1994**, *116*, 421−422. (c) Nagano, H.; Kuno, Y. *J. Chem. Soc., Chem. Commun.* **1994**, 987. (d) Rück, K.; Kunz, H. *Synthesis* **1993**, 1018. (e) Nishida, M.; Ueyama, E.; Hayashi, H.; Ohtake, Y.; Yamaura, Y.; Yanaginuma, E.; Yonemitsu, O.; Nishida, A.; Kawahara, N. *J. Am. Chem. Soc.* **1994**, *116*, 6455. (f) Sibi, M. P.; Ji, J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, in press.

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(6) *N*-Acylations were carried out by treatment of the sodium salt of the halomethyloxazolidinone (Sibi, M. P.; Rutherford, D.; Sharma, R. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1625) with the corresponding acid chloride.

(7) A byproduct identified as *N*-cinnamyl-4-(hydroxymethyl)-2-oxazolidinone (**1** X = OH) was isolated in 67% yield and its structure was confirmed by ^{1}H NMR, ^{13}C NMR, and elemental analysis.

(8) Photoisomerization of the enoyl double bond was observed during the reaction; see: Lewis, F. D.; Elbert, J. E.; Upthagrove, A. L.; Hale, P. D. *J. Org. Chem.* **1991**, *56*, 553.

(9) For discussions on conformational preference in *N*-acyloxazolidinone and oxazolidinines, see: (a) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238. (b) Kanemasa, S.; Onimura, K. *Tetrahedron* **1992**, *48*, 8631, 8645. (c) Sibi, M. P.; Jasperse, C. P.; Ji, J. *J. Am. Chem. Soc.* **1995**, *117*, 10779 and references cited therein.

(10) The formation of **3** as the major product (entry 7, Table 1) is surprising in light of the slower hydrogen atom transfer rates with TTMSS as compared to those with Bu$_3$SnH. For kinetic data, see: Chatgilialoglu, C.; Dickhaut, J.; Giese, B. *J. Org. Chem.* **1991**, *56*, 6399.

(11) For examples of dependence of stereoselectivity on different hydrogen atom donors, see: (a) Lowinger, T. B.; Weiler, L. *J. Org. Chem.* **1992**, *57*, 6099. (b) Apeloig, Y.; Nakash, M. *J. Am. Chem. Soc.* **1994**, *116*, 10781.

(12) For discussion on organotin halides as Lewis acids, see: (a) Spencer, J. N.; Ganunis, T.; Zafar, A.; Eppley, H.; Otter, S.; Coley, M.; Yoder, C. H. *J. Organomet. Chem.* **1990**, *389*, 295. (b) Yoder, C. H.; Coley, S. M.; Kneizys, S. P.; Spencer, J. N. *J. Organomet. Chem.* **1989**, *362*, 59. (c) Spencer, J. N.; Belser, R. B.; Moyer, S. R.; Haines, R. E.; Distravalo, M. A.; Yoder, C. H. *Organometallics* **1986**, *5*, 118. (d) Srikrishna, A.; Viswajanani, R. *Synlett* **1994**, 95. For a study on the influence of bis(tributyltin) oxide on radical cyclizations, see Maxwell, B. J.; Tsanaktsidis, J. *J. Chem. Soc., Chem. Commun.* **1994**, 533.

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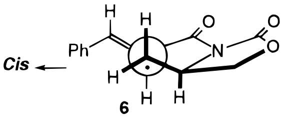
Table 1. Radical Cyclization of **1** and **2**[a]

entry	X	M–H	additive	react cond	added over time (h)	isolated yield (%)	
						3 (E:Z)[b]	**4** (de %)[c]
1	I	Bu_3SnH		rt	100	17[d] (100:0)	0
2	I	Bu_3SnH		rt/$h\nu$	20	87 (50:50)	0
3	I	$(TMS)_3SiH$		rt/$h\nu$	20	72 (71:29)	0
4	I	Bu_3SnH		80 °C	5	24 (100:0)	61 (>97)
5	I	Bu_3SnH		80 °C	20	0	82 (>97)
6	I	Ph_3SnH		80 °C	20	0	87 (88)
7	I	$(TMS)_3SiH$		80 °C	20	78 (100:0)	13 (87)
8	I	$(TMS)_3SiH$	Bu_3SnCl[e]	80 °C	20	0	87 (>97)
9	I	$(TMS)_3SiH$	Bu_3SnCl[f]	80 °C	20	0	82 (86)
10	I	$(TMS)_3SiH$	Me_3SnCl[e]	80 °C	20	0	82 (>97)
11	I	$(TMS)_3SiH$	Me_3SnBr[e]	80 °C	20	0	80 (>97)
12	I	$(TMS)_3SiH$	Bu_2SnCl_2[e]	80 °C	20	0	87 (91)
13	Br	Bu_3SnH		80 °C	20	0	78 (59)
14	Br	Bu_3SnH	Bu_3SnCl[e]	80 °C	20	0	87 (92)
15	I	Bu_3SnH	$MgBr_2{\cdot}OEt_2$	rt/$h\nu$	20	49 (57:43)[g]	0
16	I	Bu_3SnH	Et_2AlCl	rt/$h\nu$	20	50 (50:50)[h]	0
17	I	Bu_3SnH	Bu_3SnCl	rt/$h\nu$	20	50 (52:48)	21 (91)
18	I	$(TMS)_3SiH$	Bu_3SnCl	rt/$h\nu$	20	60 (60:40)	14 (86)

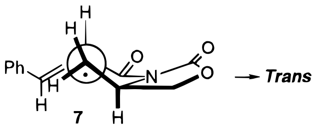
[a] Reaction conditions: to a solution of **1** or **2** (0.5 mmol) and additive (if used) in benzene (50 mL) under N_2 was added a benzene solution (10 mL) of MH (0.75 mmol) and AIBN (0.15 mmol) via syringe pump over the indicated time and temperature. [b] The E:Z ratio was determined by ^{1}H NMR. [c] de's were determined by ^{1}H NMR integration of the crude reaction mixture. [d] Reference 7. [e] 1 equiv. [f] 0.4 equiv. [g] 26% of starting material was recovered. [h] 30% of starting material was recovered.

product **4** was formed (entries 17 and 18). Since the stronger Lewis acids provide the *syn* conformer **C**,[13] the Lewis acid strength must affect the reaction outcome. Chelation by the strong Lewis acids leads to electronic perturbation and/or lower conformational flexibility, which reduce the cyclization rates. On the other hand, the organotin Lewis acid weakly coordinates and allows for the 5-*exo* cyclization.

We present here a working hypothesis for the stereoselectivity observed in the transformation of **1** to **4**. Cyclization leading to the major *cis* diastereomer occurs via the pseudoboat conformer **6**, in which the α,*β*-unsaturated unit is twisted from an idealized *syn*-(*s*)-(*Z*) geometry [conformer **C**].[14] An alternative chairlike transition state **7**, which would lead to the *trans* product, is less stable due to eclipsing interactions. The organotin halide Lewis acids enhance chemoselectivity due to chelation; however, the reason for their effect on diastereoselectivity is unclear.



6



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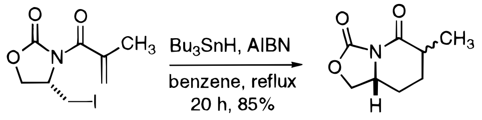
Treatment of oxazolidinone **8** under the standard radical cyclization conditions furnished only the 6-*endo* product **9** as a mixture of diastereomers (2.8:1) in 85% yield (eq 1).[15] We suggest that α-substitution leads to reaction via a rotamer of type **D** furnishing the observed 6-*endo* product.



8 **9** (1)

In conclusion, we have shown for the first time that different rotamers of *N*-enoyloxazolidinones undergo unique reactions with high chemo-, regio-, and stereoselectivity. The use of an organotin Lewis acid for enhancement of chemo- and stereoselectivity in radical reactions has also been established for the first time. The extension of these studies and investigation of Lewis acid additives in radical reactions are currently underway.

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Supporting Information Available: Experimental procedures and characterization data for compounds **1**–**5, 8**, and **9** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(13) For structural information on Lewis acid coordination to *N*-acyloxazolidinones, see: (a) Castellino, S. *J. Org. Chem.* **1990**, *55*, 5197. (b) Castellino, S.; Dwight, W. J. *J. Am. Chem. Soc.* **1993**, *115*, 2986.

(14) Energy minimization calculations (PC Model, MMX) indicate that the α,*β*-unsaturated unit is twisted ~50° from the *syn*-(*s*)-(*Z*) conformer **C** and the nitrogen atom is nearly planar. For a discussion of transition states in intramolecular radical cyclizations, see: Spellmeyer, D. C.; Houk, K. *J. Org. Chem.* **1987**, *52*, 959.

(15) Cyclization of the parent *N*-acryloyloxazolidinone under a variety of reaction conditions gave only conjugate addition or polymeric products.