

How Do Analogous α -Chloroenamides and α -Iodoenamides Give Different Product Distributions in 5-*Endo* Radical Cyclizations?

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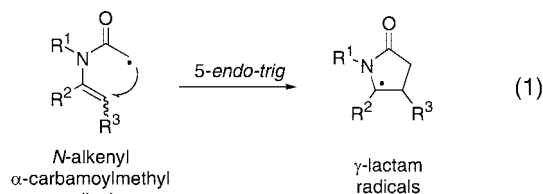
Abstract: 5-*Endo* cyclizations of *N*-alkenyl carbamoylmethyl radicals provide γ -lactam radicals, which in turn evolve to reduced or non-reduced (alkene) products depending on reagents and reaction conditions. Several groups have made surprising observations that chlorides are better radical precursors than iodides in such cyclizations. Here is described a detailed study of tin and silicon hydride-mediated radical cyclizations of *N*-benzyl-2-halo-*N*-cyclohex-1-enylacetamides. The ratios of directly reduced, cyclized/reduced, and cyclized/non-reduced products depend not only on the reaction conditions and reducing reagent but also on the precursor. Prior explanations for the precursor-dependent product ratios based on amide rotamer effects are ruled out. The precursor-dependent behavior is further dissected into two different effects: (1) the ratio of cyclized/reduced products to cyclized/non-reduced products depends on the ability of the radical precursor to react with the product γ -lactam radical in competition with tin hydride (iodides can compete, chlorides cannot), and (2) the occurrence of large amounts of directly reduced (noncyclized) products in the case of iodides is attributed to a competing ionic chain reaction by which the precursor is reductively deiodinated with HI. This side reaction is not available to chlorides, thereby explaining why the chlorides are better precursors in such reactions. The ability of the iodides to provide cyclized products can be largely restored by adding base. The chlorides and iodides then become complementary precursors, with chlorides giving largely cyclized/reduced products and iodides giving largely cyclized/non-reduced products.

Introduction

Once regarded as curiosities, 5-*endo* radical cyclizations are increasingly important in synthetic radical chemistry.^{1,2,3,4} While they are not as general as 5-*exo* and 6-*exo* cyclizations, 5-*endo* radical cyclizations are surprisingly useful in a diverse assortment of settings, and suitable substrates often contain second-

row elements or multiple sp^2 -hybridized atoms between the radical precursor and acceptor.

The 5-*endo* cyclization of *N*-vinyl carbamoylmethyl radicals to provide γ -lactam radicals, first described by Ikeda and Ishibashi, is probably the most common of all classes of 5-*endo* cyclizations (eq 1). Such radicals can be generated from *N*-vinyl- α -haloamides (α -haloenamides) either under reductive conditions to provide saturated lactams, or under oxidative conditions to produce heteroatom-substituted or unsaturated lactams. This reaction has been developed extensively into a general approach to γ -lactams by Ishibashi, Parsons, Clark, and others.⁵



During the course of this development, Ishibashi and co-workers made unusual observations in comparing cyclizations of α -chloro-, α -bromo-, and α -iodoenamide precursors **1a–c** of the same radical. These precursors gave very different product ratios, and surprisingly, the iodide **1c** was by far the poorest

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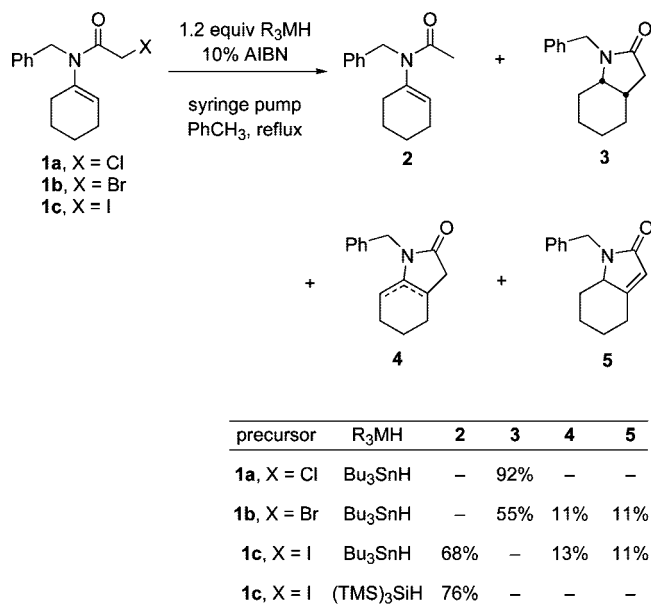


Figure 1. Ishibashi's cyclizations of α -haloamides **1a–c** with tin and silicon hydrides.

performer of the three.⁶ Several of the key results published in the provocatively titled article “Is an Iodine Atom Almighty as a Leaving Group for Bu₃SnH-Mediated Radical Cyclization?” are summarized in Figure 1.

Slow syringe pump addition of Bu₃SnH to α -haloenamides **1a–c** at reflux in toluene provided a mixture of the expected cyclized/reduced product **3** along with cyclized/non-reduced products **4** and **5** and directly reduced (non-cyclized) product **2**. The product distributions varied as a function of the radical precursor. Cyclization of chloride **1a** was highly efficient and provided only cyclized/reduced product **3** in 92% yield. Bromide **1b** again provided only cyclized products, but this time reduced product **3** (55%) was accompanied by 11% of each of the cyclized/non-reduced products **4** and **5**. In stark contrast, the iodide **1c** provided none of the standard cyclized/reduced product **3**, and the cyclized/non-reduced products **4** and **5** were produced in 13% and 11% yields, respectively. By far the major product was directly reduced **2** in 68% yield. Changing the reducing agent for **1c** to tris(trimethylsilyl)silicon hydride ((TMS)₃SiH)⁷ did not make matters better, but worse; no cyclized products were formed at all, and **2** was isolated in 76% yield. Both Ishibashi and Parsons have described similar trends in related substrates, so the observations are not isolated.⁴

These unusual observations of high amounts of directly reduced product **2** led Ishibashi and co-workers to the apparently inescapable conclusion that “an iodine atom is not the best radical leaving group for radical cyclizations of α -haloenamides”.⁶ But how can this be? It is well known that iodides are exceptionally more reactive (10⁴–10⁶ times) than related chlorides toward Bu₃Sn[•], (TMS)₃Si[•], and related radicals.⁸ If the iodine atom is the most reactive leaving group, then why is it not the best leaving group for forming the cyclized products?

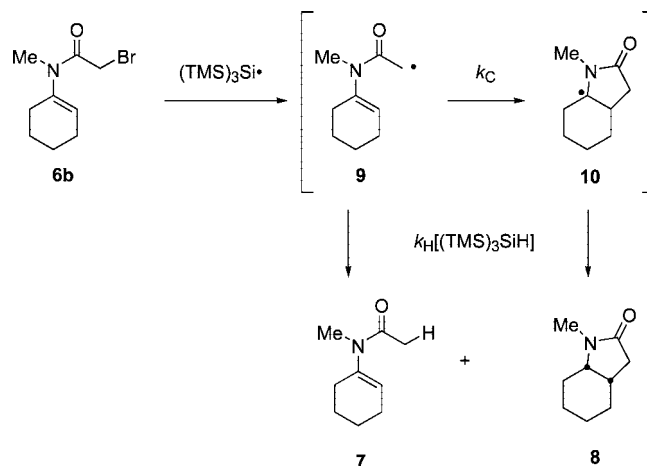


Figure 2. Chatgililoglu's cyclizations of α -bromoamide **1b** under pseudo-first-order conditions with (TMS)₃SiH.

To further add to the quandary, Chatgililoglu and workers reported a thorough study of cyclization of bromoenamide **6b**, which is closely related to **1b** (*N*-methyl instead of *N*-benzyl).^{2a} Under standard pseudo-first-order conditions for competition radical kinetics (large excess of (TMS)₃SiH), they observed only the cyclized/reduced product **8** and the directly reduced product **7** (Figure 2). The ratios of these products varied in a standard fashion as a function of silane concentration, thereby allowing the calculation of the rate constant for 5-*endo* cyclization of **9** to **10** as $2 \times 10^4 \text{ s}^{-1}$ at 25 °C.

The contrast between Chatgililoglu's well-behaved product ratios and Ishibashi's unexpected ones focuses attention on the unusual behavior of the different radical precursors and derived radicals under syringe pump addition conditions. To provide more insight into this behavior, we undertook a detailed study of both the radical precursors and the radical reactions under strictly controlled conditions. Our observations suggest that the ratios of reduced/non-reduced products are controlled by concentration effects on bimolecular reactions (hydrogen transfer and oxidation) that compete for cyclized radicals. We further identify conditions where formation of the directly reduced product **2** from iodide **1c** can be suppressed, so there is no longer any basis to conclude that iodides are somehow less reactive than chlorides. Instead, we suggest a non-radical path that is responsible for the formation of the directly reduced products from iodides.

Results and Discussion

Structures and Rotation Dynamics of the Radical Precursors.

Rates of rapid radical cyclization reactions can exceed those of amide bond rotations,⁹ so the starting rotamer ratio of an amide radical precursor can have a significant effect on downstream radical reactions. Along these lines, Ishibashi and co-workers postulated that chloride **1a** might have a ground-state preference for *E*-amide rotamer **1aE** (Figure 3), and thus its derived radical **11E** would be prone to cyclization.³ In contrast, iodide **1c** might

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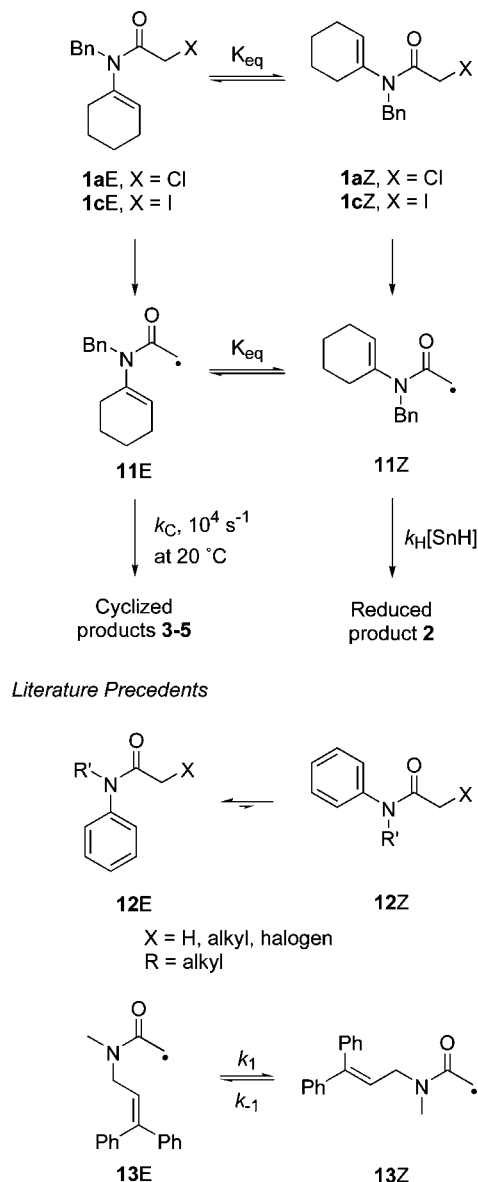


Figure 3. Amide rotamers of **1a–c** and derived radicals.

have an increased ground-state preference for *Z*-rotamer **1cZ**, the derived radical of which **11Z** would be prone to reduction.

In addition to the assumption that the chloride **1a** and the iodide **1c** have significantly different ground-state rotamer ratios, this proposal assumes that radicals **11E** and **11Z** are not in equilibrium on the time scale of their onward reactions. There is reason to doubt that either of these assumptions is valid. First, *N*-alkyl anilides are reasonable models of these enamides because they have an *N*–C(sp²) bond (to an aromatic ring rather than a cyclohexenyl group). Such molecules are well known to exhibit a healthy preference for the *E*-rotamer (see **12E** in Figure 3);¹⁰ thus, the postulate that iodide **1c** has significant amounts of *Z*-rotamer at equilibrium lacks support. Second, Newcomb and co-workers have measured the rate constant for rotation of

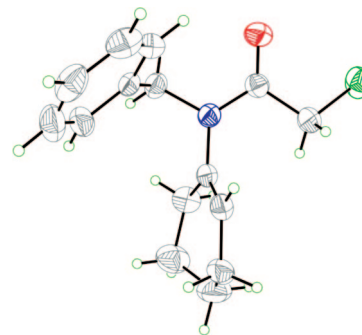


Figure 4. X-ray crystal structure of chloroenamide **1c**.

amide radical **13E/13Z** (Figure 3) as $5 \times 10^5 \text{ s}^{-1}$ at 20 °C,¹¹ and this is about 25 times faster than the rate constant for cyclization of radical **9** measured by Chatgililoglu.^{2a} Radicals **9/11** and **13** are not directly comparable;¹² however, the slow rate of cyclization of **11E** relative to rotation suggests that rotamer populations might not be important in such 5-*endo* cyclizations.

To provide more information on the starting rotamer ratios of **1a–c** and their rotational dynamics, we undertook spectroscopic and crystallographic studies. The ¹H NMR spectra of **1a–c** at 300 MHz in CDCl₃ were all very similar and exhibited a single resonance for each chemically different proton or group of protons. Thus, either the compounds exist largely as a single amide rotamer, or they exist as two rotamers in rapid equilibrium on the NMR time scale. The latter explanation seems unlikely since α-halo amides have rotation barriers typical of other amides,¹³ and thus the C–N rotation barriers of **1a–c** are expected to be in the range of 15–17 kcal/mol.¹⁴ Processes with barriers of this height are slow on the NMR time scale and give rise to broadened or, more typically, well-separated resonances in room-temperature spectra.

While there is no evidence for amide *E/Z*-rotamers in the NMR spectra, pairs of protons on several methylene groups (for example, the benzyl and halocarbonyl CH₂ groups) exhibited sharp, well-resolved signals. This resolution of diastereotopic protons shows that the molecules are axially chiral in solution, with a twisted *N*-alkenyl bond. This twisting is expected from the analogy to anilides.¹⁰

So **1a–c** exist in solution as predominantly a single amide rotamer, and the analogy to anilides suggests that this is the *E*-rotamer. We supported this conclusion by crystallizing chloride **1a** and solving its X-ray structure.¹⁵ As shown in Figure 4, the amide bond in the crystal exists in the *E*-rotamer. As expected from the NMR results,¹⁰ **1c** exhibits axial chirality. The planes of the amide and the *N*-alkenyl group are nearly

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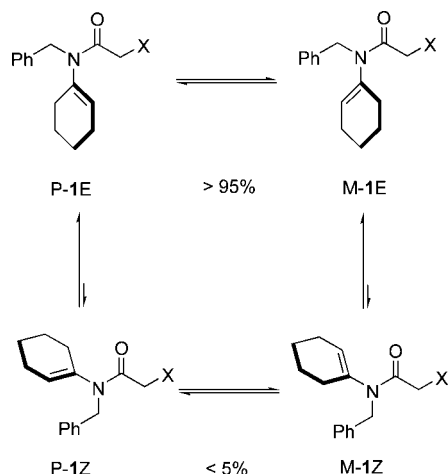


Figure 5. Rotational profile of the amide C–N and *N*-alkenyl bonds of **1a–c** (X = Cl, Br, I).

orthogonal, with a dihedral angle of about 74°. The crystal was composed of a single enantiomer of **1c**, and the presence of the chlorine atom aided in solution of the absolute configuration of the molecule as *P*.

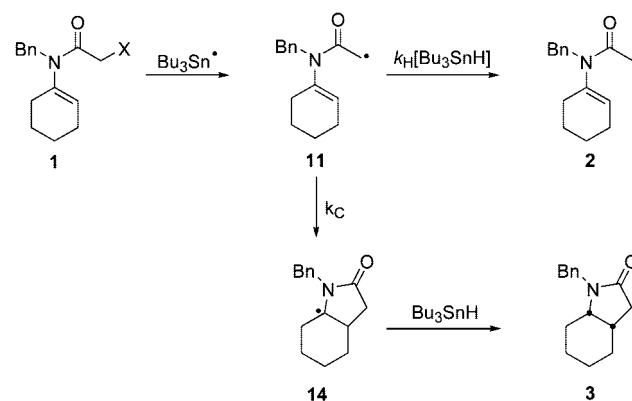
Collectively, these results provide a general picture of the rotational properties of enamides like **1a–c**, and this picture (Figure 5) closely resembles that of the related axially chiral anilides. Enamides **1** exist predominately as *E*-rotamers, with the population of *Z*-rotamer unknown but certainly less than 5% in non-polar solvents. In turn, each amide rotamer exists as a pair of enantiomers that interconvert slowly on the NMR time scale by *N*-alkenyl bond rotation.

Assuming that the *E* and *Z* amide rotamers of the halides should have comparable reactivity toward Bu₃Sn[•], there should be a strong preference for formation of radical **11E** (Figure 3) in reactions of all three halides **1a–c**. Further, Chatgililoglu has calculated that radicals related to **11E** are considerably more stable than their *Z*-rotamers (by >4 kcal/mol).^{2a} If **11Z** does form in small amounts, then its best option is probably rotation to **11E**. Accordingly, the contribution of products derived from radical **11Z** in Figure 3 can be neglected; **11E** is likely the immediate precursor of all cyclized and reduced products.

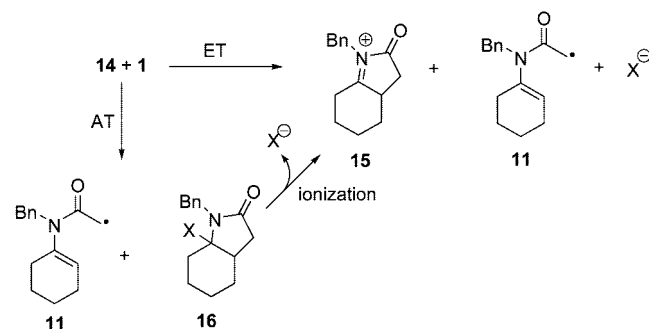
Competition Kinetics. Clearly the suggestion that differing results in the radical cyclizations of chloride **1a** and iodide **1c** originate from conformational differences in these precursors is untenable. Accordingly, upon reaction with Bu₃Sn[•], chloride **1a** and iodide **1c** (and presumably bromide **1b**) should generate the same radical. To test this notion, we conducted a series of competition kinetics experiments¹⁶ by reducing the radical precursors **1a–c** with fixed concentrations of Bu₃SnH and measuring the product ratios by gas chromatography (GC).

The mechanistic scheme for the competition kinetics experiments is shown in Figure 6. Halogen abstraction from precursor **1** generates radical **11**, which then partitions in the key competition step between direct bimolecular reduction by tin hydride to give **2** and unimolecular, 5-*endo* cyclization to give **14**. Radical **14** can be reduced by tin hydride to give the reduced/cyclized product **3**. Or, it can react with a molecule of radical precursor **1** either by direct electron transfer (ET) or by halogen atom transfer (AT),¹⁷ followed by ionization of **16** to give acyliminium ion **15**. In turn, **15** loses a proton to give enamides

Formation of Reduced Products



Formation of Non-Reduced Products by Reactions of **1** and **14**



Alkene Formation by Deprotonation of **15**

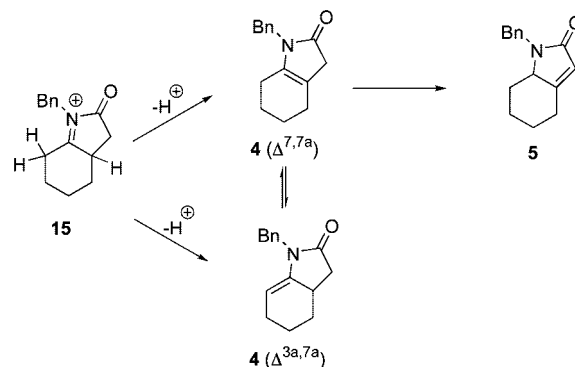


Figure 6. Mechanisms for product formation in radical cyclizations of **1a–c**.

4 ($\Delta^{7,7a}$ and/or $\Delta^{3a,7a}$ isomers), and subsequent double-bond migration provides isomerized product **5**.

Syntheses of authentic samples and characterization of all the products in Figure 6 are described in the Supporting Information. The isomers of **4** were very sensitive to equilibration in solution or on silica gel, and they were always isolated

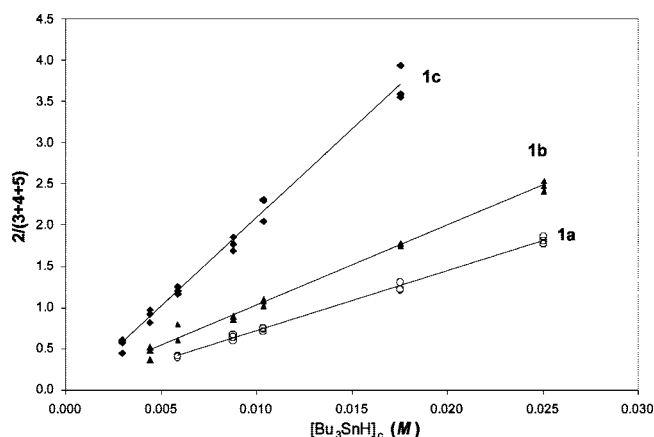
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Table 1. Product Distributions in Competitive Cyclizations of **1a–c** with Bu_3SnH^a

halide	$[\text{Bu}_3\text{SnH}]_0$, mM	% yield ^b				cyc:red ^c
		2	3	4 + 5	total	
1a	10.0	15	33	2	60	70:30
	15.0	22	32	3	57	61:39
	17.8	29	36	3	68	57:43
	30.0	39	29	2	70	44:66
	42.9	56	28	2	86	35:65
1b	7.5	18	34	5	57	68:32
	10.0	22	29	5	56	61:39
	15.0	38	39	4	81	53:47
	17.8	41	35	4	80	49:51
	30.0	52	27	3	82	36:64
1c	42.9	55	20	2	77	29:71
	7.5	31	16	18	65	52:48
	10.0	33	13	14	60	45:55
	15.0	46	12	14	72	36:64
	17.8	55	11	14	80	31:69
	30.0	68	9	10	87	22:78

^a Conditions: the appropriate substrate (1.0 equiv), Bu_3SnH (1.2 equiv), and AIBN (0.2 equiv) in toluene were combined in a sealed tube and heated at 110 °C for 3 h. ^b GC yield, using octadecane as an internal standard. Yields are an average of three trials. ^c Ratio of (3 + 4 + 5) to 2.

**Figure 7.** Kinetic plot of data in Table 1.

in a 2.3/1 ratio of $\Delta^{7,7a}$ to $\Delta^{3a,7a}$. Also, all the alkenes **4** ($\Delta^{7,7a}$), **4** ($\Delta^{3a,7a}$), and **5** exhibited a single, coincident peak on GC analysis, so it is possible that equilibration occurs here as well. Thus, the GC analysis gives only a total yield of the three alkene products without giving ratios. This is convenient because all three products derive from the same pathway. Since **5** was the only alkene isolated in pure form, its response factor was determined and used to quantify the collective alkene peak in the gas chromatogram.

Competition experiments were conducted by reacting an α -haloenamamide **1a–c** (0.025 mmol), Bu_3SnH (1.2 equiv), and azobisisobutyronitrile (AIBN, 0.2 equiv) in toluene at 110 °C in a sealed tube for 3 h. The mixture was cooled, the tube was cracked, and the sample was analyzed by GC against octadecane as an internal standard. Full details on the experiments and analyses are provided in the Supporting Information. All reactions were reproducible and clean, product peaks were well defined, and no significant other products were formed, even though mass balances were not quantitative (60–87%).

The results of this series of experiments are summarized in Table 1 and plotted in Figure 7 in the usual format (ratio of directly reduced product to the sum of all cyclized products versus tin hydride concentration). Several trends are apparent.

As the Bu_3SnH concentration was increased, the ratio of reduced product **2** to cyclized products **4–6** increased for all substrates. Likewise, the total mass balance tended to increase as well. The starting iodide **1c** was consumed in all experiments, but small amounts of bromide **1b** and chloride **1a** remained in the experiments at lower tin hydride concentrations (even though all the tin hydride was consumed).

The ratio of the cyclized/reduced product **3** to the cyclized/non-reduced products **4** and **5** depended on the halogen atom of the precursor, in qualitative agreement with Ishibashi's results. Regardless of the tin hydride concentration, chloride **1a** gave about a 15/1 ratio of reduced to non-reduced products, while the ratio with bromide **1b** was 9/1, and that with iodide **1c** was 1/1. These results suggest that acyliminium ion **15** is not reduced ionically by Bu_3SnH to give **3**, but instead loses a proton to give alkenes **4**.

The plots of the ratio of the reduced product **2** to the combined cyclized products **3–5** versus the tin hydride provide further information. The experiments are not pseudo-first-order in tin hydride, so the mean tin hydride concentrations were used for the plots, as recommended by Newcomb.¹⁶ In principle, the three precursors should give the same radical, so the lines in Figure 7 should coincide. In practice, they do not. There is a 3-fold difference in the slopes of the lines for the chloride **1a** and the iodide **1c**.

Like Chatgililoglu,² we approximated the rate constant for hydrogen abstraction by the carbamoylmethyl radical **11** from Bu_3SnH as $9.3 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ at 383 K. This provides the following rate constants for cyclization of radical **11** as a function of precursor: from chloride **1a**, $1.3 \times 10^5 \text{ s}^{-1}$; from bromide **1b**, $5.1 \times 10^4 \text{ s}^{-1}$; and from iodide **1c**, $4.0 \times 10^4 \text{ s}^{-1}$. These compare well to the more accurately determined rate constant for related radical **9** (Figure 2) at 383 K, $5.1 \times 10^4 \text{ s}^{-1}$. This rate constant was measured starting from the bromide precursor only.^{2a}

The mechanistic scenario in Figure 6 does not allow for differing rate constants for 5-*endo* cyclization as a function of radical precursor. However, we stress that the measured differences, while outside experimental error, are rather small. For example, if a stoichiometric amount of tin hydride is not consumed in the formation of alkenes **4**, then the mean concentration of this reagent will be higher in the experiments with the bromide **1b** and especially the iodide **1c**. More reduced product **2** will form, and the (apparent) cyclization rate constant will be lower.

Further, the lines in Figure 7 all converge at low tin hydride concentration, suggesting that all the precursors should behave similarly in syringe pump experiments. This is not at all in line with Ishibashi's results from preparative syringe pump addition. The lines also share a common y-intercept of approximately zero, which in turn supports the postulate that the 5-*endo* cyclization is not reversible. Finally, the similar slope of the lines coupled with the halogen-dependent ratios of reduced/non-reduced cyclized products supports the notion that the pathways for formation of these products diverge after the cyclization, as proposed in Figure 6.

Ishibashi and co-workers also reported that cyclization of iodide **1c** by syringe pump addition of tributyltin hydride was improved by the addition of excess tributyltin chloride (Bu_3SnCl) or other tin compounds, but addition of tributyltin iodide (Bu_3SnI) did not have much effect. It was suggested that Bu_3SnCl could act as a Lewis acid, altering the rotational behavior of the radical precursor **1c** or the reactivity of the

Table 2. Product Distributions in Competitive Cyclizations of **1c** with Bu₃SnH (10 mM) in the Presence of Tin Halides^a

additive	equiv	% yield ^b				cyc:red ^c
		2	3	4 + 5	total	
none		13	14	33	60	45:55
Bu ₃ SnCl	1.0	10	9	33	52	36:64
Bu ₃ SnCl	3.0	3	8	25	36	31:69
Bu ₃ SnCl	5.0	9	9	33	51	35:65
Bu ₃ SnI	1.0	13	12	34	59	42:58
Bu ₃ SnI	2.0	14	9	32	55	42:58
Bu ₃ SnI	3.0	13	8	31	52	41:59

^a Conditions: the appropriate substrate (1.0 equiv), Bu₃SnH (1.2 equiv), Bu₃SnX additive, and AIBN (0.2 equiv) in toluene were combined in a sealed tube and heated at 110 °C for 3 h. ^b GC yield, using octadecane as an internal standard. Yields are an average of three trials. ^c Ratio of (3 + 4 + 5) to 2.

radical **11**. Sibi has suggested that tin halides can alter the rotamer population of *N*-enoyloxazolidinones,¹⁸ and other Lewis acids are known to affect radical reactions of α -halocarbonyl compounds.¹⁹

To learn the effects of Bu₃SnCl on the radical precursor, we recorded the ¹H NMR spectrum of a 1/1 mixture of **1c** and Bu₃SnCl in CDCl₃; no shifts in any resonances were observed, suggesting that little or no complexation occurred. To probe for halogen exchange,²⁰ we heated a toluene solution of **1c** and 5 equiv of Bu₃SnCl at reflux for 5 h, but only a small amount of conversion to chloride **1a** (<5%) was observed by GC. In contrast, addition of 5% tetrabutylammonium iodide (Bu₄NI) promoted rapid halogen exchange,²⁰ and the ratio of **1a**/**1c** decreased to a level of about 1.4/1 over 1 h. No further change occurred, suggesting that equilibrium was reached. These results suggest that, in the presence of a halide ion source, tin halides and α -haloamides readily exchange their halogen atoms.

To learn the effect of the tin halides on the cyclization under fixed tin hydride concentration experiments, we conducted a second series of cyclizations of iodide **1c** with increasing amounts of Bu₃SnCl (1, 3, or 5 equiv) and Bu₃SnI (1, 2, or 3 equiv). In every experiment, the initial concentration of Bu₃SnH was 10 mM. The results of these experiments, summarized in Table 2, show that the additives have little or no effect on the product distributions. Indeed, the cyclization of **1c** under conditions of fixed tin hydride concentrations is very reproducible.

These experiments do not support the notion that Bu₃SnCl can function as a Lewis acid toward either the starting iodide **1c** or the intermediate radical **11**. However, it does seem plausible that some of the effect observed by Ishibashi was due to conversion of iodide **1c** to chloride **1a** under the syringe pump addition experiments. Since the tin halides are apparently not functioning as Lewis acids, we decided not to pursue this line of investigation further.

The mechanism in Figure 6 suggests that increasing the concentration of the iodide **1c** while holding the tin hydride concentration constant will provide more non-reduced cyclized products **4/5** relative to reduced cyclized product **3**. To test this notion, we conducted three experiments with limiting quantities of Bu₃SnH (1 equiv, 0.01 M) and increasing amounts (1.0, 1.5,

Table 3. Product Ratios in Cyclization of Variable Concentrations of **1a** at Fixed Tin Hydride Concentrations^a

equiv of 1c	% yield ^b				recovered 1c (equiv)	cyc:red ^c	ox:cyc ^d
	2	3	4 + 5	total			
1.00	21	12	13	46	0.00	54:46	1.1:1
1.50	26	6	15	47	0.15	45:55	2.5:1
2.00	28	4	16	48	0.46	29:71	4.0:1

^a Conditions: iodide **1c**, Bu₃SnH (1.0 equiv), and AIBN (0.2 equiv) in toluene were combined in a sealed tube and heated at 110 °C for 3 h. ^b GC yield, using octadecane as an internal standard. Yields are an average of three trials. Bu₃SnH was the limiting reagent. ^c Ratio of (3 + 4 + 5) to 2. ^d Ratio of (4 + 5) to 3.

and 2.0 equiv) of iodide **1c** and measured the product yields by GC as above. The results of these experiments are summarized in Table 3. Total mass balances in all three experiments were modest (41–47%), but again no new products were observed by GC.

As projected, the ratio of non-reduced/reduced cyclized products ([4 + 5]/2) increased from 1.1/1 to 2.5/1 to 4.0/1 as the substrate concentration increased. Interestingly, however, the ratio of cyclized to reduced products ([3 + 4 + 5]/2) also changed (from 54/46 to 45/55 to 29/71), even though the tin hydride concentration remained constant. Finally, in both of the experiments where tin hydride was used in deficiency relative to the iodide **1c**, the percentage of iodide consumed exceeded the amount of tin hydride added. A control experiment showed that the iodide **1c** was stable in refluxing toluene, so simple thermal decomposition is ruled out. These results suggest that the ET/AT process in Figure 6 can, at least to some extent, operate as an independent chain and consume starting iodide without consuming tin hydride.

With the two groups of experiments in Tables 1 and 3, we have independently probed two separate features of syringe pump experiments: (1) that the tin hydride concentration is very low (Table 1 results) and (2) that the tin hydride is present in deficient amounts relative to the starting material throughout the experiment (Table 3 results). The collective results suggest that it is the deficiency of tin hydride, and not its low concentration, that produces the unusual results with the iodide precursors.

Cation and Radical Trapping Experiments. We next conducted cyclization experiments with one substrate designed to trap a cyclized cation²¹ and one designed to trap a cyclized radical. Neither trapping experiment succeeded as planned, but together they supported Ishibashi's observations and provided more clues about the unusual behavior of the iodides. The syntheses of the substrates **17a,c,d** and products and the analyses of the reactions are described in the Supporting Information.

Cyclizations of the cation-trap substrates, chloride **17a** and iodide **17c**, were conducted by syringe pump addition of a toluene solution of Bu₃SnH (1.2 equiv) and AIBN (0.1 equiv) over 2 h to a refluxing solution of the precursor in toluene (Figure 8). This procedure is similar to that followed by Ishibashi and different from the competition experiments above. After cooling and solvent evaporation, the crude product mixture was treated with aqueous KF^{22a} and then purified by flash chromatography to provide isolated yields of individual products. In

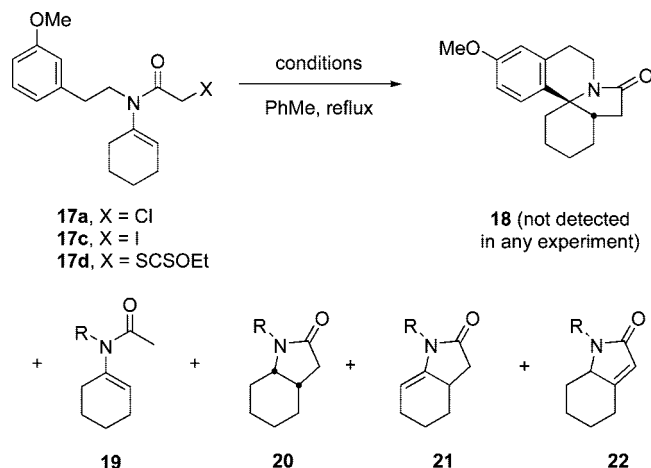
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19-22, R = *m*-MeOC₆H₄CH₂CH₂-

precursor	conditions	19	20	21	22
17a	Bu ₃ SnH	10%	75%	—	—
17c	Bu ₃ SnH	12%	—	9%	43%
17c ^a	Bu ₃ SnH	14%	—	13%	45%
17d	Bu ₃ SnH	13%	62%	—	—
17d	lauroyl per.	—	—	—	67%

a) in refluxing 1,2-dichloroethane

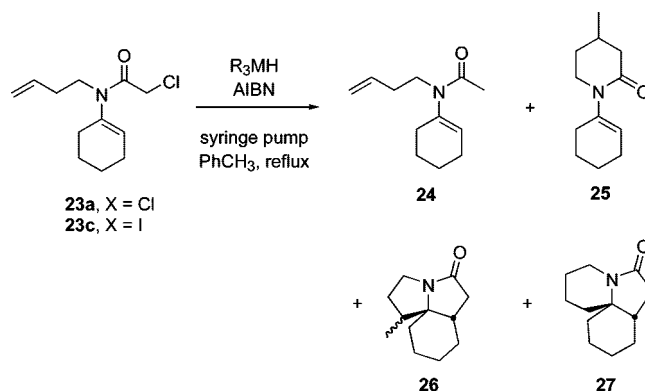
Figure 8. Product distributions in cyclizations of cation-trap substrates 17.

no case did we detect any of the cation cyclization product **18**; however, the observed results resembled those of Ishibashi's preparative syringe pump experiments rather than our fixed concentration kinetic experiments.

Cyclization of chloride **17a** provided a 75% yield of reduced/cyclized product **20** along with 10% of the directly reduced product **19**; alkenes **21** and **22** were not detected. Reductive cyclization of the xanthate **17d** under the same conditions provided similar results; cyclized product **20** was isolated in 62% yield and reduced product **19** in 13% yield. Alkenes **21** and **22** were not observed. In contrast, non-reductive cyclization of **17d** with lauroyl peroxide^{4j,23} provided only conjugated alkene **22** in 67% isolated yield.

The cyclization of iodide **17c** in toluene occurred in lower yield, providing 9% of **21**, 43% of **22**, and about 12% of **19**. The disappearance of **20** at the expense of **21** and **22** is expected because the ET mechanism is favored over reduction at low tin hydride concentration. A similar experiment in refluxing dichloroethane provided **22** in 45% yield, along with 15% reduced **19**.

It is likely that cation intermediates are involved in the formation of **21** and **22**, so trapping by Friedel–Crafts reaction to give **18** is too slow to compete with deprotonation of the intermediate acyl iminium ion. This assertion was supported by an experiment in which **22** was exposed to a catalytic amount



precursor	R ₃ MH, time	24	25	26	27
23a	Bu ₃ SnH, 3 h	6%	5%	14%	51%
23c	Bu ₃ SnH, 3 h	83%	tr	tr	tr
23c	Bu ₃ SnH, 6 h	75%	tr	tr	tr
23c	(TMS) ₃ SiH, 6 h	maj. ^a	—	—	—

Isolated yields; tr is trace product detected but not isolated

a) major product detected in a complex mixture

Figure 9. Product distributions in cyclization of radical-trap substrates 23.

of *p*-TsOH in refluxing dichloroethane for 12 h.²⁴ This produced tetracycle **18** in 82% yield, along with 12% recovered **22**. Clearly cationic cyclization is possible, but the acyl iminium ion must be generated reversibly many times before it can occur. Under the conditions of the radical cyclization, cationic cyclization cannot compete with deprotonation.

As substrates for radical trapping, we selected chloride **23a** and iodide **23c** because the chloride is already a known compound, the cyclization of which has been studied by Ishibashi.^{4a} Cyclizations of **23a,c** were again conducted by syringe pump addition as described above. Products were isolated by flash chromatography over KF/silica gel,^{22b} and the yields are summarized in Figure 9. The Bu₃SnH-mediated cyclization of **23a** went generally as expected, providing 65% of the tandem cyclization products **26** (5-*exo*) and **27** (6-*endo*), along with a small amount of directly reduced **24** (6%) and competing cyclization product **25** (5%). (This results from 6-*exo* radical cyclization to the *N*-butenyl group in competition with 5-*endo* cyclization to the enamide.) Ishibashi reported a similar combined yield of tandem cyclized products (59%), though there was more of the 5-*exo* and less of the 6-*endo* product.

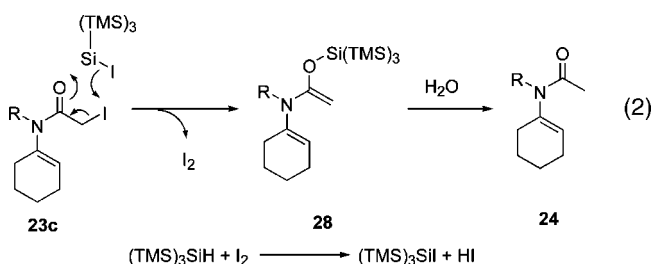
Most shocking were the experiments with iodide **23c**: syringe pump addition of Bu₃SnH over either 3 or 6 h provided almost exclusively the reductively deiodinated product **24** (83% and 75%, respectively), with only traces of the other products. We also tried to reduce **23c** with (TMS)₃SiH, but as soon as the addition was begun, the color of the reaction mixture turned deep red. Insertion of pH paper into this reaction mixture showed that it was highly acidic. These observations suggest that diiodine (I₂) and HI are present. This reaction mixture was very difficult to purify, producing **24** still contaminated with silicon-containing byproducts. Again however, no cyclized products

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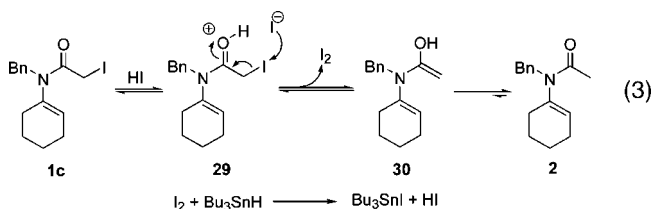
were apparent. These results are qualitatively consistent with those reported by Ishibashi for the reaction of **1c** with $(\text{TMS})_3\text{SiH}$.

A speculative mechanism for the formation of diiodine in reactions with $(\text{TMS})_3\text{SiH}$ is shown in eq 2. The standard reaction of $(\text{TMS})_3\text{SiH}$ with **23c** should produce $(\text{TMS})_3\text{SiI}$, which in turn could react with precursor **23c** by a precedented ionic mechanism²⁵ to provide **28** and I_2 . Hydrolysis of **28** during workup would provide reduced product **24**. In turn, HI could be formed either by reaction of $(\text{TMS})_3\text{SiH}$ with diiodine or through the ET/AT pathway as in Figure 6. The reaction of **23c** with $(\text{TMS})_3\text{SiH}$ is complex, so these are not selective and efficient pathways, but they are possible nonetheless. Chloride **23a** presumably cannot react with the silyl chloride by this pathway, and instead a standard radical chain ensues.



Effects of Acid and Base. We had assumed that any HI generated during the reactions of these iodoesters would be consumed by an acid/base reaction with the stannane or silane. However, these acid/base reactions may not be sufficiently fast to suppress other reactions, especially under syringe pump addition conditions (where the concentration of the hydride is always very low). The above results led us to consider that HI might instead react ionically with the starting iodoamide by the pathway shown in eq 3.²⁶ The resulting molecule of diiodine that formed would then react with tin hydride to give Bu_3SnI and another molecule of HI. The result is a non-radical chain that reduces the iodoamide while oxidizing the tin hydride.

To test this idea, we attempted to reductively deiodinate **1c** under several different ionic conditions, and the results of these experiments are summarized in eq 3. Treatment of **1c** with Bu_3SnI alone gave no reaction, but it was slowly deiodinated over 24 h on exposure to camphorsulfonic acid (CSA) to provide **2** in 53% yield. Treatment of **1c** with both Bu_4NI and CSA provided a 68% yield of **2** in only 2 h. Accordingly, a combination of an acid and iodide ion can apparently reduce **1c** in a non-radical process. Interestingly, heating of **1c** with CSA and Bu_3SnI resulted in no reaction, suggesting that the tin iodide is not a good source of iodide ion.



Attempts to deiodinate **1c**

conditions	2
Bu_3SnI	—
CSA, 24 h	54%
Bu_4NI , CSA, 2 h	68%

Table 4. Product Distribution in Reductive Cyclizations of **1c** with Base Additives^a

additive	% yield ^b				total	cyc:red ^c
	2	3	4	5		
—	35	4	13	21	73	52:48
pyridine	5	13	60	3	81	94:6
2,6-lutidine	5	4	45	22	76	93:7
Cs_2CO_3	—	4	44	5	53	>99:1
K_2CO_3	—	10	41	20	71	>99:1
Proton Sponge	—	—	32	—	32	>99:1

^a Conditions: a solution of Bu_3SnH (1.2 equiv) and AIBN (0.1 equiv) in toluene (12 mM in Bu_3SnH) was added via syringe pump to a refluxing mixture of the amide **1c** in toluene (10 mM) and additive over 3 h. ^b Isolated yield after 10% KF/silica column chromatography. ^c Ratio of (**3** + **4** + **5**) to **2**.

To test whether the proposed ionic pathway for reductive deiodination of **1c** could be suppressed by base, we conducted a series of cyclization reactions under typical syringe pump conditions in the presence of base additives. The crude products were purified by chromatography on 10% (w/w) KF/silica gel, and the isolated product yields from these reactions are shown in Table 4. In the control experiment with no additive, we obtained significant amounts of directly reduced product **2** (35%), alongside cyclized/non-reduced products **4** and **5**. In a similar experiment, Ishibashi observed even more reduced product than we did (68%, see Figure 1), but syringe pump addition experiments are often difficult to reproduce quantitatively. Qualitatively, the formation of relatively large amounts of **2** at very low tin hydride concentrations, is again consistent with Ishibashi's results.

All of the bases suppressed or eliminated the formation of the directly reduced product **2** while providing increased yields of the alkene ET/AT products, especially **4**. Pyridine provided the highest yield of **4** (60%), although there was still 5% of the reductively deiodinated products **2**. Apparently, pyridine is not a strong enough base to cause double bond migration of the initial products **4** to give **5**. Inexpensive potassium carbonate also performed well, providing a 61% combined yield of alkene products **4** and **5** with no directly reduced products. Cesium carbonate and especially Proton Sponge gave lower yields along with decomposition products.

Conclusions

The results reported herein provide a basis for understanding the unusual behavior of α -iodoenamides (and α -bromoenamides) in 5-*endo* cyclizations. The rotational features of the chloride, bromide, and iodide precursors are very similar, and they do not play a role in the differing product ratios. Furthermore, the unusual behavior is caused not because the iodide is a poorer radical precursor compared to chloride, but instead because it is a much better one. In the case of chlorides, a standard tin hydride chain occurs. In the case of iodides, the ET/AT process that ensues from the reaction of the cyclized radical with its own radical precursor competes with standard reaction of the radical with Bu_3SnH . The ET/AT process is a radical chain that generates HI. In turn, this HI can set off a non-radical chain

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deiodination process for the formation of the directly reduced product **2**. It is this HI-mediated background process that makes it appear as if the iodide is a poorer radical precursor than the chloride.

The ET/AT process and the non-radical chain that it sets off are most efficient under syringe pump addition conditions because they can both propagate while there is a deficiency of tin hydride. This explains why the syringe pump addition experiments with the iodides give results very different from those obtained with the low-concentration experiments with stoichiometric quantities of tin hydride. The addition of a suitable base neutralizes the HI that is formed in the ET/AT process with the iodides, thereby suppressing the ionic reduction path and restoring the radical cyclization efficiency of the iodoenamides. Nonetheless, the chloroenamide and iodoenamide precursors are still complementary because of the divergence after the 5-*endo* cyclization. The chloride provides primarily the reductively cyclized products through a standard tin hydride

chain, while the iodide provides predominately the alkene products via the ET/AT chain.

The light shed by this mechanistic study will allow more controlled and predictable applications of the important class of 5-*endo* cyclizations of haloenamides. Furthermore, the observed behavior is not tied to the type of radical cyclization (5-*endo*) that occurs, but instead to the type of reducing radical that is formed (an α -amido radical). So, the results can be extrapolated to other types of radical reactions as well.

Acknowledgment. We thank the National Science Foundation for funding this work. This paper is dedicated to the memory of Prof. Albert I. Meyers.

Supporting Information Available: Experimental procedures, compound characterization, and crystallographic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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