

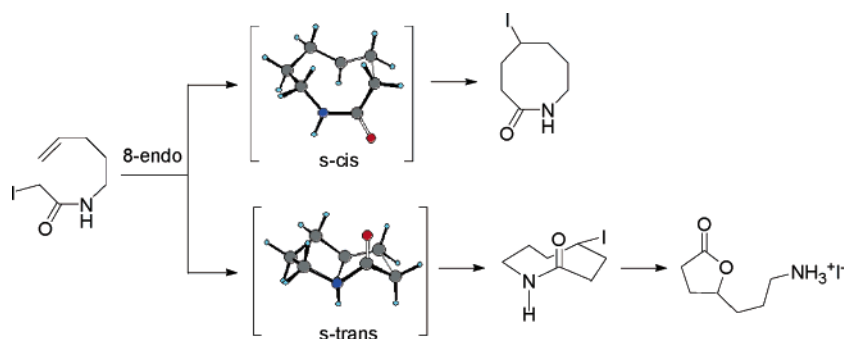
## 8-Endo versus 7-Exo Cyclization of $\alpha$ -Carbamoyl Radicals. A Combination of Experimental and Theoretical Studies

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Atom transfer radical cyclization reactions of *N*-(4-pentenyl)iodoacetamides were investigated. The reactions were efficiently promoted by  $\text{BF}_3 \cdot \text{OEt}_2$ . For *N*-alkenyl-substituted iodoamides, excellent regioselectivity in favor of 8-endo cyclization was observed, while both 7-exo and 8-endo cyclization products were formed with the 8-endo cyclization preferred in the cases of *N*-(2-allylphenyl)-substituted iodoamides. Density functional theory calculations at the B3LYP/6-31G\* level revealed that both the *s*-trans and the *s*-cis conformational transition structures were feasible for the 8-endo cyclization of *N*-alkenyl-substituted  $\alpha$ -carbamoyl radicals while 7-exo transition structures were much less stable. For the cyclization of *N*-(2-allylphenyl)-substituted  $\alpha$ -carbamoyl radicals, the transition structures for 8-endo and 7-exo cyclizations were of comparable energy. These results were in excellent agreement with the experimental observations.

### Introduction

The past 2 decades have witnessed a rapid progress in radical chemistry toward organic synthesis.<sup>1</sup> Radical cyclizations, in particular, have received enormous attention.<sup>1,2</sup> Among them, cyclization of  $\alpha$ -carbamoyl radicals has been demonstrated to be a viable means for the construction of lactam skeletons and thus of great

potential in organic synthesis.<sup>1,3</sup> However, most of the studies were concentrated on the cyclization in a 5-exo mode, while little is known of the 8-endo or 7-exo cyclization. The only examples were the  $\text{Bu}_3\text{SnH/AIBN}$ -initiated cyclization reactions of haloamides **1** reported by Ikeda and co-workers, which showed that the ratios of 7-exo and 8-endo products **2** and **3** depended strongly on the types of radical precursors (Scheme 1).<sup>4</sup> For example, the dichloroamide **1** ( $X = Y = \text{Cl}$ ) generated exclusive 7-exo cyclization product **2**, while the bistiophenylamide **1** ( $X = Y = \text{PhS}$ ) furnished the corresponding 8-endo cyclization product **3**.

Owing to the significance of seven- and eight-membered lactams in organic synthesis,<sup>5</sup> we looked into these reactions in detail. We report here that the atom transfer

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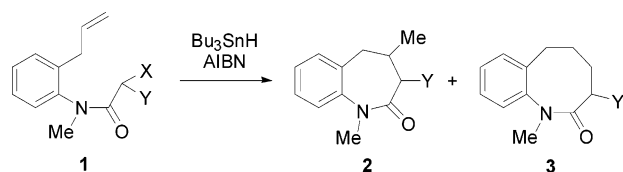
<sup>‡</sup> Peking University.

<sup>§</sup> Hong Kong University of Science and Technology.

(1) For review articles, see: (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon: Oxford, UK, 1986. (b) Curran, D. P. *Synthesis* **1988**, 417 and 489. (c) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (d) Melikyan, G. G. *Synthesis* **1993**, 833. (e) Iqbal, J.; Bhatia, B.; Nayyar, N. K. *Chem. Rev.* **1994**, *94*, 519. (f) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339. (g) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, Germany, 1996. (h) Gansauer, A.; Bluhm, H. *Chem. Rev.* **2000**, *100*, 2771. (i) *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001. (j) Sibi, M. P.; Manyem, S.; Zimmerman, J. *Chem. Rev.* **2003**, *103*, 3263.

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## SCHEME 1



radical cyclization reactions of *N*-(4-pentenyl)iodoacetamides (**4** and **6**) could be efficiently promoted by  $\text{BF}_3 \cdot \text{OEt}_2$ . Furthermore, density functional calculations at the B3LYP/6-31G\* level were employed to locate the possible transition structures for the cyclizations, which in turn provided a detailed understanding of the mechanism of the  $\alpha$ -carbamoyl radical cyclization.

## Results

Halogen atom transfer methods with  $(\text{Bu}_3\text{Sn})_2$  or  $\text{BEt}_3$  as the initiator developed by Curran et al. have been well demonstrated to be a unique and effective method for the cyclizations of  $\alpha$ -carbonyl radicals.<sup>6</sup> Thus, we prepared *N*-(4-pentenyl)iodoacetamide (**4a**) as the model substrate for the investigation of 7-exo or 8-endo cyclization of  $\alpha$ -carbamoyl radicals. For the ease of comparison, the substrate concentration was set at 0.03 M. Direct photostimulation of **4a** with  $(\text{Bu}_3\text{Sn})_2$  (10 mol %) in benzene or  $\text{CH}_2\text{Cl}_2$  at room temperature did not give any expected cyclization product while the starting material remained unchanged. When the reaction was carried out at refluxing temperature of benzene (80 °C), the reaction proceeded very slowly, and the initiator  $(\text{Bu}_3\text{Sn})_2$  was consumed within a few hours. Photostimulation of **4a** with 50 mol % of  $(\text{Bu}_3\text{Sn})_2$  at 80 °C for 1 day gave the cyclized product **5a** in only 26% yield along with a significant amount of unidentified decomposition products. To accelerate the cyclization, we turned to Lewis acids for help as they have recently been widely used in promoting radical reactions.<sup>7</sup> Among the Lewis acids screened,  $\text{BF}_3 \cdot \text{OEt}_2$  gave the best results. With the addition of 2 equiv of  $\text{BF}_3 \cdot \text{OEt}_2$  at room temperature, the solution became cloudy immediately and within 30 min the mixture turned to clear again while some precipitate

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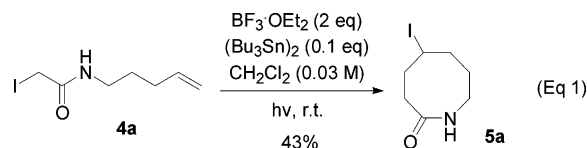
(7) For review articles, see: (a) Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2562. (b) Guerin, B.; Ogilvie, W. W.; Guindon, Y. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds; Wiley-VCH: Weinheim, 2001; Vol. 1, p 441.

TABLE 1. 8-Endo Cyclization of Iodoamides **4a–e**

substrate	product	yield(%) <sup>a</sup>
		43
		51
		59
		34
		49

<sup>a</sup> Isolated yield based on **4**.

was formed at the bottom of the flask. <sup>1</sup>H NMR monitoring indicated that the starting material **4a** was all consumed. After filtration, the filtrate was checked by <sup>1</sup>H NMR, which showed that only the 8-endo cyclization product **5a** was formed while no corresponding 7-exo cyclization product could be detected. After removal of the tin-containing residue, **5a** was achieved in 43% isolated yield (eq 1).



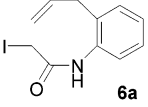
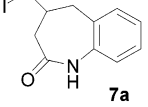
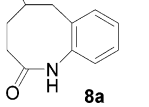
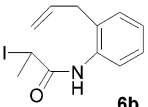
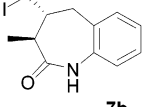
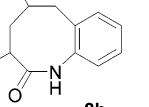
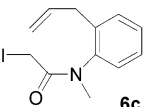
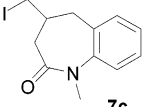
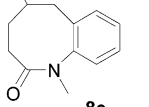
Other Lewis acids such as  $\text{Mg}(\text{OTf})_2$ ,  $\text{Zn}(\text{OTf})_2$  or  $\text{Yb}(\text{OTf})_3$  did not show a significant effect on the reaction. This is probably because of their poor solubility in solvents such as  $\text{CH}_2\text{Cl}_2$  or benzene.<sup>8</sup>

Thus, a number of unsaturated iodoamides **4a–e** were photostimulated in the presence of  $\text{BF}_3 \cdot \text{OEt}_2$  (2 equiv) and  $(\text{Bu}_3\text{Sn})_2$  (0.1 equiv) in  $\text{CH}_2\text{Cl}_2$  at room temperature and the results are summarized in Table 1. In all the cases, only the 8-endo cyclization products **5a–e** were obtained, indicating a high regioselectivity in these cyclization reactions.

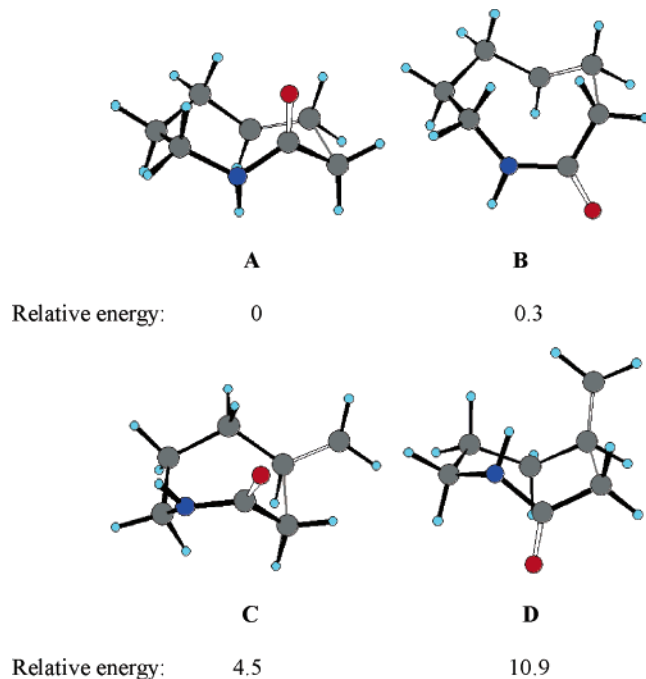
We also prepared phenyl-containing iodoamides **6a–c** and subjected them to the above reaction conditions as shown in eq 1. The results are presented in Table 2. In contrast to the reactions of **4a–e**, both 7-exo cyclization products **7a–c** and 8-endo cyclization products **8a–c**

(8) For similar discussions, see: (a) Wang, J.; Li, C. *J. Org. Chem.* **2002**, *67*, 1271. (b) Fang, X.; Xia, H.; Yu, H.; Dong, X.; Chen, M.; Wang, Q.; Tao, F.; Li, C. *J. Org. Chem.* **2002**, *67*, 8481.

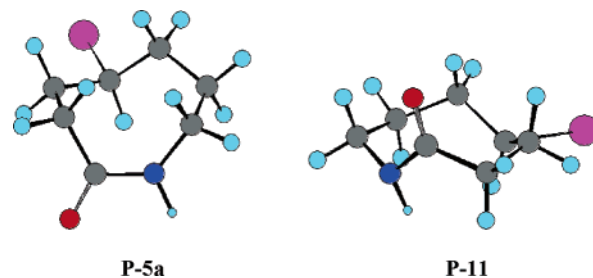
TABLE 2. 8-Endo/7-Exo Cyclization of Iodoamides 6a–c

substrate	product	yield (%) <sup>a</sup> (7 : 8)
	 + 	70 (28:72)
	 + 	100 (39:61) <sup>b</sup>
	 + 	73 (27:73)

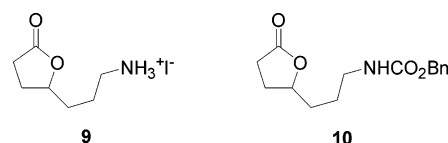
<sup>a</sup> Isolated yield based on **6**. <sup>b</sup> cis:trans = 2.5:1 for **8b**.

FIGURE 1. Calculated structures of the transition structures for the cyclization of **4a** with relative free energies in kcal/mol.

were formed. The ratios of **7** to **8** were about 1:2 with the 8-endo cyclization products preferred. Moreover, the overall yields in the reactions of **6a–c** were much higher than in the cases of **4a–e**. The configurations of the cyclization products **5b**, **5d** and **7b** were unambiguously established by their NOESY spectra. The NOESY spectra of **5b** and **5d** also showed strong NOE between H-3 and H-8 protons, indicating that *s*-cis conformations were preferred for the eight-membered lactams in the solution. Moreover, the X-ray crystal structures of eight-membered lactams **5a** and **8a**, shown in Scheme 2, both possess the *s*-cis boat-chair-like conformations.

FIGURE 2. Calculated structures of **5a** and **11**.

The difference in cyclization yield between Tables 1 and 2 prompted us to recheck the reactions of **4**. We noticed that, while there was always some precipitate formed in the reactions of **4a–e**, no precipitate was observed in the reactions of **6a–c**. Initially we thought that the precipitate might be the radical oligomers of **4a–e**. However, when the precipitate formed in the reaction of **4a** was collected and treated with water at room temperature, it quickly dissolved and the <sup>1</sup>H NMR analysis showed that compound **9** was formed. The formation of **9** was further confirmed by its reaction with benzyl chloroformate in the presence of triethylamine as the base to afford the expected product **10**, which was unambiguously characterized. Compound **10** was thus obtained in 26% yield based on the original substrate **4a**. This result clearly indicated that the precipitate formed in the reactions of **4** was not the radical oligomers because the hydrolysis of the oligomers of **4a** required elevated temperature in hydrochloric acid.<sup>9</sup>



### Calculations and Discussion

The different reaction phenomena between substrates **4** and **6** remained to be explained. To gain more insight into the cyclization behavior of  $\alpha$ -carbamoyl radicals, we turned to quantum mechanics calculations for help, which have been shown to be an increasingly important tool in modeling radical reactions and mechanisms.<sup>10,11</sup>

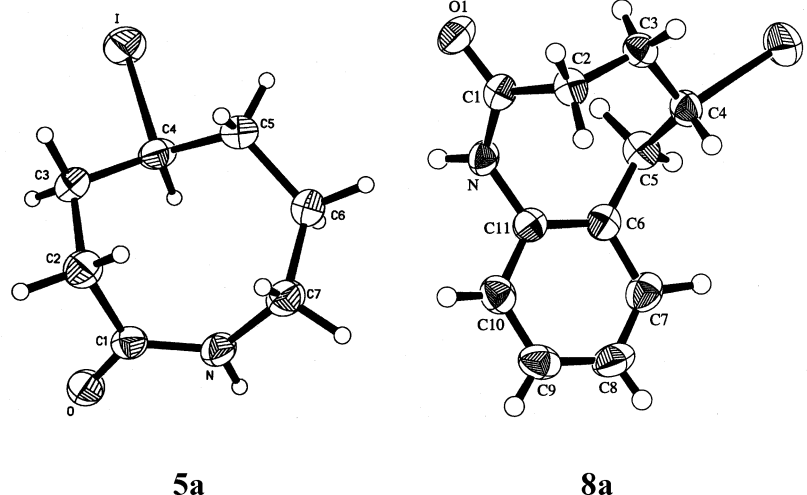
All calculations were carried out with the Gaussian98 programs.<sup>12</sup> The structures of the transition structures were searched and optimized with Becke's three-parameter hybrid exchange functional and the Lee–Yang–Parr correlation functional (B3LYP)<sup>13</sup> and the 6-31G\* basis sets.<sup>14</sup> Vibration frequency calculations were also performed to characterize the transition structures, having

(9) Liu, L.; Wang, X.; Li, C. *Org. Lett.* **2003**, *5*, 361.

(10) For review articles on use of calculations in radical reactions, see: (a) Eksterowicz, J. E.; Houk, K. N. *Chem. Rev.* **1993**, *93*, 2439.

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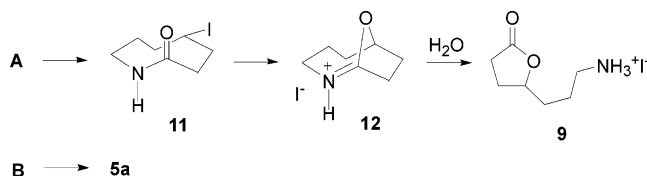
SCHEME 2. ORTEP Diagrams of **5a** and **8a**

only one imaginary frequency. In the following discussions all energies are in terms of free energy.

The calculated transition structures for the cyclization of **4a** are listed in Figure 1. The optimized transition structures for 8-endo cyclization are shown as **A** and **B**. Conformation **A** is in an s-trans chair-chair-like conformation, while **B** is in an s-cis boat-chair-like conformation. **A** is calculated to be about 0.3 kcal/mol more stable than **B**. This implies that both s-cis and s-trans 8-endo cyclization products can be formed. The two optimized transition structures for 7-exo cyclization are presented as **C** and **D**. Structure **C** in an s-cis conformation has a boat-boat-like conformation and is at least 4 kcal/mol higher in energy than structures **A** and **B**. Structure **D**, which is in an s-trans conformation, is found to be very unstable and is about 10.9 kcal/mol less stable than **A**. The C(3)–C(2)–N(1)–C(8) dihedral angle in **D** is about 123°, indicating a severe distortion of the amide moiety from planarity.

Thus, the calculation results indicate that only 8-endo cyclization occurs while 7-exo cyclization of **4a** is highly unlikely, which is in excellent agreement with our experimental observations. In addition, the results suggest that both s-cis and s-trans eight-membered lactams should be formed. Then how to account for the experimental fact that only the s-cis lactam was observed? It should be noted that iodolactam **5a**, once formed, was quite stable under the experimental conditions. Deliberate treatment of **5a** with  $\text{BF}_3 \cdot \text{OEt}_2$  at room temperature did not give any decomposition product, indicating that

SCHEME 3



lactone **9** could not result from the decomposition of **5a** in an s-cis conformation.

We propose that the s-trans lactam (**11**) was indeed formed in the experiment. However, it underwent an intramolecular  $\text{S}_{\text{N}}2$  reaction to give an tetrahydrofuran iminium salt **12**, as shown in Scheme 3.<sup>15</sup> Compound **12**, which exists as a precipitate, is converted into soluble salt **9** when treated with water.<sup>15</sup>

We then performed the calculations of lactams **5a** and **11** at the B3LYP/6-31G\* level. The calculated structures are presented in Figure 2. The calculation results show that the s-cis lactam **5a** and its s-trans isomer **11** have only about 0.9 kcal/mol difference in energy. The calculated structure of **5a** (**P-5a**) is almost identical to its X-ray structure shown in Scheme 2. An examination of the structure of **P-11** reveals that the carbonyl oxygen lies at the backside of the C(5)–I bond and is quite close to the C-5 carbon (3.68 Å). Thus, intramolecular nucleophilic attack of the carbonyl oxygen at the C-5 carbon readily occurs.

We also performed the similar calculations on the cyclization of *N*-(2,2-dimethyl-4-pentenyl)iodoacetamides **4c**. The results showed that the s-trans and the s-cis conformational transition structures for 8-endo cyclization of **4c** were very close in free energy with the s-cis structure more stable by 0.1 kcal/mol, while the transition structures for 7-exo cyclization of **4c** were at least 3.5 kcal/mol higher in energy than those for 8-endo cyclization (see Supporting Information for details). These results coincided well with those of **4a** as shown above.

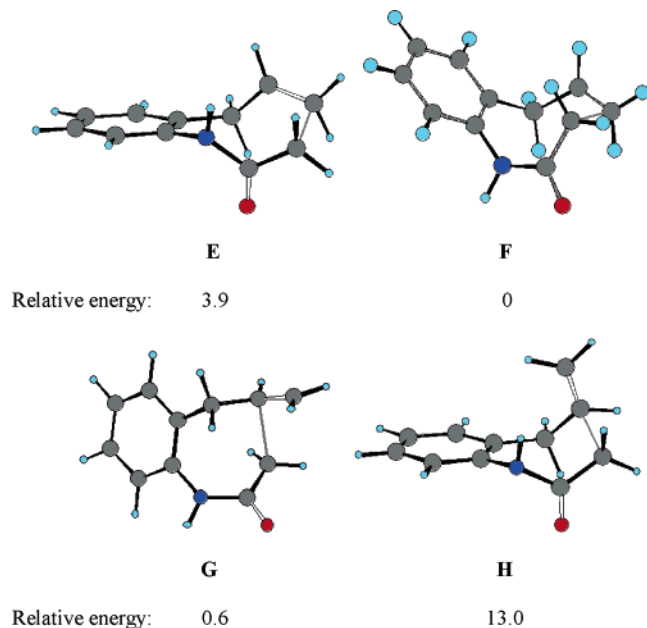
The calculations on **4a** and **4c** are also in good qualitative agreement with the experimental data. As the s-cis transition structure **B** is less stable than the s-trans

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(14) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257.

(15) For similar reactions, see: Barton, D. H. R.; Beckwith, A. L. J.; Goosen, A. *J. Chem. Soc.* **1965**, 181.



**FIGURE 3.** Calculated structures of the transition structures for the cyclization of **6a** with relative free energies in kcal/mol.

transition structure **A**, the yield of the cyclized product **5a** is lower than 50%. On the other hand, the *s*-cis transition structure is more stable than the *s*-trans transition structure for 8-endo cyclization of **4c**. As a result, the yield of **5c** is higher (59%).

The above discussion illustrates that the 8-endo cyclization of *N*-alkenyl-substituted  $\alpha$ -carbamoyl radicals is a highly regioselective and efficient process. Although the decomposition of the cyclization product via the *s*-trans conformational transition structure appears unsatisfactory in a synthetic point of view, it can be envisioned that, with the development of an appropriate radical precursor or initiation system, the *s*-trans lactams formed might rotate to the more stable *s*-cis lactams rather than decomposition to lactones, thus of more synthetic value. A similar process is the 8-endo cyclization of  $\alpha$ -ester radicals in which the *s*-cis conformational eight-membered lactones were achieved in high yield via the *s*-trans conformational transition structures.<sup>8a,16</sup>

The calculated transition structures for the cyclization of **6a** are presented in Figure 3. The two optimized transition structures for 8-endo cyclization are **E** and **F**. The *s*-trans conformational transition structure **E** is about 3.9 kcal/mol less stable than conformation **F**, which is in an *s*-cis boat-chair-like conformation. This result indicates that only **F** is the possible transition structure for the 8-endo cyclization of **6a**. The two optimized transition structures for 7-exo cyclization are **G** and **H**. The *s*-trans conformer **H** is much higher in energy than the *s*-cis conformer **G**, strongly suggesting that the 7-exo cyclization of **6a** proceeds via the *s*-cis conformational transition structure **G**. Moreover, the calculated energy of **G** is only about 0.6 kcal/mol higher than that of **F**, indicating that both 7-exo and 8-endo cyclization can

occur. The measured product ratio is consistent with this small computed energy difference between **F** and **G**.

The different behaviors between **4a** and **6a** can be readily understood based on the above calculated structures. With the phenyl substitution, the N(2)–C(2)–C(3)–C(4) dihedral angle has to be 0°. This causes tremendous ring strain in *s*-trans structures **E** and **H**. For example, the C(4)–N(8)–C(9)–O(10) dihedral angle is about 175° in both the *s*-cis structures **F** and **G**, while the corresponding dihedral angle is about –29° in **E** and is much larger (–55°) in **H**.

The calculations on the cyclization of **6a** may also provide a reasonable explanation to Ikeda's results shown in Scheme 1.<sup>5</sup> As the relative energy between the transition structures **F** (8-endo) and **G** (7-exo) is small, it can be envisioned that different  $\alpha$ -substituents (**Y**) in **1** may alter the relative energies in different directions, thus resulting in different regioselectivities.

## Conclusion

The chemistry detailed above has demonstrated that 8-endo cyclization of *N*-alkenyl  $\alpha$ -carbamoyl radicals is an intrinsically favored process, which can be efficiently promoted by Lewis acid BF<sub>3</sub>·OEt<sub>2</sub>. Theoretical investigation reveals that the cyclization of *N*-alkenyl  $\alpha$ -carbamoyl radicals proceeds with excellent regioselectivity in favor of the 8-endo mode via both the *s*-cis and the *s*-trans conformational transition structures. These understanding should be of important implication in the further development of  $\alpha$ -carbamoyl radical-based synthetic methodology.

## Experimental Section

**Typical Procedure for the Cyclization Reactions of *N*-(4-Pentenyl)iodoacetamides.** Bis(tributyltin) (29  $\mu$ L, 0.06 mmol) was added to the mixture of *N*-(4-pentenyl)iodoacetamide **4a** (151 mg, 0.6 mmol) and BF<sub>3</sub>·OEt<sub>2</sub> (0.14 mL, 1.2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and the solution was photostimulated with stirring at room temperature for 30 min with the aid of a 300 W sunlamp. The resulting mixture was filtered and the precipitate was collected for further reaction. The filtrate was washed with saturated Na<sub>2</sub>CO<sub>3</sub> (10 mL) and then dried over anhydrous MgSO<sub>4</sub>. After removal of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel with ethyl acetate as the eluent to give pure **5a** as a yellow solid. Yield: 65 mg (43%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  1.63–1.86 (2H, m), 1.94–2.18 (2H, m), 2.22–2.30 (1H, m), 2.43–2.49 (2H, m), 2.61–2.70 (1H, m), 3.21–3.31 (1H, m), 3.41–3.54 (1H, m), 4.52–4.59 (1H, m), 6.15 (1H, br); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  31.2, 32.3, 32.7, 34.8, 40.5, 41.0, 176.4; IR (film)  $\nu$  (cm<sup>-1</sup>) 3195, 1678; EIMS *m/z* (rel intensity) 253 (M<sup>+</sup>, 2), 126 (100), 97 (16), 81 (10), 69 (18), 55 (29), 41 (25); HRMS calcd for C<sub>7</sub>H<sub>12</sub>INO 252.9964, found 252.9982. The structure was further confirmed by its X-ray diffraction analysis.

The precipitate collected above was dissolved in water (5 mL) and THF (10 mL). The mixture was cooled to 0 °C and K<sub>2</sub>CO<sub>3</sub> powder was added until the pH was close to 9. Benzyl chloroformate (102 mg, 0.6 mmol) was added and the mixture was stirred at 0 °C for 2 h and then at room temperature for 4 h. The resulting mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3  $\times$  10 mL). The combined organic phase was washed with brine (10 mL) and then dried over anhydrous MgSO<sub>4</sub>. After removal of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel with ethyl acetate/hexane (1:1, v:v) as the eluent to give pure **10** as a colorless liquid. Yield: 43 mg (26% based on **4a**). <sup>1</sup>H NMR (300

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MHz, CDCl<sub>3</sub>)  $\delta$  1.64–1.86 (5H, m), 2.27–2.33 (1H, m), 2.52 (2H, dd,  $J = 9.0, 7.2$  Hz), 3.19–3.30 (2H, m), 4.44–4.52 (1H, m), 4.90 (1H, br), 5.10 (2H, s), 7.28–7.37 (5H, m); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  26.0, 27.9, 28.7, 32.6, 40.4, 66.6, 80.4, 128.0, 128.1, 128.4, 136.5, 156.4, 177.0; IR (film)  $\nu$  (cm<sup>-1</sup>) 3341, 1769, 1702, 1529; EIMS  $m/z$  (rel intensity) 277 (M<sup>+</sup>, 1), 170 (9), 126 (20), 108 (62), 91 (100), 85 (10), 65 (12), 41 (5). Anal. Calcd for C<sub>15</sub>H<sub>19</sub>NO<sub>4</sub>: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.88; H, 6.73; N, 5.01.

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**Note Added after ASAP Publication.** Bu<sub>3</sub>SnH was incorrectly listed as (Bu<sub>3</sub>Sn)<sub>2</sub> in the text description of Scheme 1 in the version published ASAP January 26, 2005. The corrected version was published ASAP January 28, 2005.

**Supporting Information Available:** Characterization of **4–10**; computational results on the structures **A–H**, **P-5a**, **P-11** and on the transition structures for the cyclization of **4c**; and X-ray crystal structures of **5a** and **8a** in CIF format. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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