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Published on Web 02/01/2010

Efficient Regio- and Stereoselective Formation of Azocan-2-ones via 8-*Endo* Cyclization of α-Carbamoyl Radicals

Xinqiang Fang, Kun Liu, and Chaozhong Li*

Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, P. R. China

Received October 5, 2009; E-mail: clig@mail.sioc.ac.cn

Abstract: The iodine-atom-transfer 8-*endo* cyclization of α-carbamoyl radicals was investigated experimentally and theoretically. With the aid of $Mg(ClO_4)_2$ and a bis(oxazoline) ligand, *N*-ethoxycarbonyl-substituted *N*-(pent-4-enyl)-2-iodoalkanamides underwent 8-*endo* cyclization leading to the formation of only the corresponding 3,5-*trans*-substituted azocan-2-ones in excellent yields. Similarly, the $BF_3 \cdot OEt_2$/H_2O-promoted reactions of *N*-ethoxycarbonyl-*N*-(2-allylaryl)-2-iodoalkanamides afforded exclusively the benzazocanone products with a 3,5-*cis* configuration in high yields. The bidentate chelation of substrate radicals not only significantly improved the efficiency of cyclization but also resulted in the change of stereochemistry of azocanone products from 3,8-*trans* to 3,8-*cis*. Theoretical calculations at the UB3LYP/6-31G* level revealed that the cyclization of *N*-carbonyl-substituted α-carbamoyl radicals occurs via the *E*-conformational transition states without the presence of a Lewis acid. On the other hand, the cyclization proceeds via the *Z*-conformational transition states when the substrates form the bidentate chelation with a Lewis acid. In both cases, the 8-*endo* cyclization is always fundamentally preferred over the corresponding 7-*exo* cyclization. The complexed radicals having the more rigid conformations also allow the better stereochemical control in the iodine-atom-abstraction step. To further understand the reactivity of α-carbamoyl radicals, the competition between the 8-*endo* and 5-*exo* cyclization was also studied. The results demonstrated that the 8-*endo* cyclization is of comparable rate to the corresponding 5-*exo* cyclization for α-carbamoyl radicals with fixed *Z*-conformational transition states. As a comparison, the 8-*endo* mode is fundamentally preferred over the 5-*exo* mode in the cyclization of NH-amide substrates because the latter requires the *Z*-conformational transition states, whereas the former proceeds via the more stable *E*-conformational transition states.

Introduction

The addition of carbon-centered radicals to C═C bonds has been firmly established as an indispensable tool for carbon−carbon bond formations.[1] The intramolecular version, in particular, provides a facile entry to various carbo- and heterocycles with unique chemo-, regio-, and stereoselectivities. This radical cyclization strategy has found wide application in the synthesis of complex natural products and medicinal agents.

Among various modes of radical cyclization, 5-*exo* and 6-*exo* cyclizations are perhaps the most extensively studied types of reactions. As a comparison, 7-*exo* and 8-*endo* radical cyclizations have received much less attention. Theoretical calculations by Beckwith and Schiesser predicted that the 8-*endo* cyclization of 7-octenyl radical is preferred over the corresponding 7-*exo* cyclization.[2] The 8-*endo* cyclizations of various types of radicals,[3−15] including alkyl,[3] aryl,[4] acyl,[5] ketyl,[6] and even amidyl radicals,[7] were later implemented with variable efficiencies and regioselectivities. Of particular concern was the

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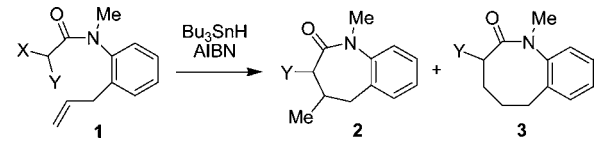
10.1021/ja9082649

cyclization of α-ester radicals,[8−12] especially those leading to the synthesis of heptanolactones.[9−12] Literature reports revealed that the 8-*endo* cyclization is fundamentally preferred over the corresponding 7-*exo* cyclization for α-ester radicals. The presence of Lewis acids such as $BF_3 \cdot OEt_2$ significantly accelerated the cyclization, providing a highly efficient entry to heptanolactones.[12] More importantly, Lee and co-workers discovered that the 8-*endo* mode was even preferred over the 5-*exo* mode in the cyclization of (α-alkoxycarbonyl)methyl radicals.[11] This was analyzed by the fact that the 5-*exo* cyclization requires the *E*-conformational (s-*cis*) transition states (TS), whereas the 8-*endo* cyclization can proceed via the more stable *Z*-conformational (s-*trans*) TS. Nevertheless, the weakness of these 8-*endo* cyclization reactions was also obvious in that poor stereoselectivity was typically observed.[12]

The examples of successful regioselective 8-*endo* cyclization of α-ester radicals certainly encouraged the development of 8-*endo* cyclization of α-carbamoyl radicals because of the structural similarity between these two types of radicals.[16] However, only a few examples could be found in the literature on the 7-*exo* versus 8-*endo* cyclization of α-carbamoyl radicals, which showed a behavior dramatically different from that of α-ester radicals.[13−15,9g] Ikeda and co-workers reported the reactions of haloamides **1** with the initiation of Bu_3SnH/AIBN

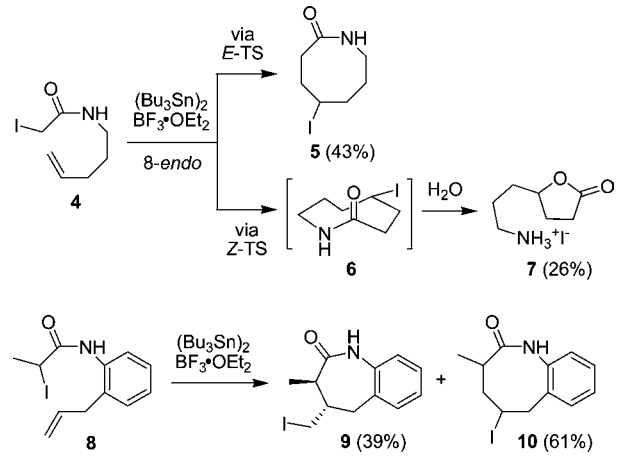
Scheme 1



(Scheme 1), in which they observed that the regioselectivity depended strongly on the types of radical precursors.[13] For example, the dichloroamides **1** (X = Y = Cl) gave exclusive 7-*exo* cyclization product **2**, whereas the bisthiophenylamide **1** (X = Y = PhS) generated the corresponding 8-*endo* cyclization product **3**.[13] Similar results were also obtained in the *N*-benzyl analogues of **1** as reported by Murphy et al.[9g] The iodine-atom-transfer radical cyclization reactions of *N*-(4-pentenyl)-2-iodoalkanamides such as **4** were later investigated by us (Scheme 2).[14] The reactions were carried out at much milder conditions (room temperature) with the promotion of $BF_3 \cdot OEt_2$. An excellent regioselectivity in favor of 8-*endo* cyclization was observed. However, the yields of azocanones (such as **5**) were only moderate, and lactones such as **7** were also generated as the side products. This phenomenon was then analyzed by our density functional calculations, which showed that the 8-*endo* cyclization could proceed via both the *Z*- and the *E*-conformational TS and that the cyclized product **6** via the *Z*-conformational TS underwent decomposition to give **7**. As a comparison, the atom-transfer cyclization of *N*-(2-allylphenyl)-2-iodoalkanamides had a high efficiency but a very poor regioselectivity. For example, the cyclization of iodide **8** afforded the mixture of benzazepinone **9** and benzazocinone **10** in about a 2:3 ratio.

A clear understanding and efficient control of the reactivity of α-carbamoyl radicals are thus required in order to develop the halogen-atom-transfer 8-*endo* α-carbamoyl radical cyclization into a useful synthetic methodology. Specifically, (1) the difference between the *Z*-conformational TS and the *E*-conformational TS in terms of the efficiency and regioselectivity of cyclization has to be understood; (2) effective control over the TS conformations is necessary to direct the cyclization to proceed as planned; (3) the substituent effect on the cyclization has to be examined on the basis of which highly stereoselective reactions might be developed; and finally, (4) to make the 8-*endo* cyclization of more synthetic value, it is highly desirable that a high degree of stereochemical control over the halogen-atom-abstraction step could be achieved, although poor stereoselectivity is typically observed in *endo*-type halogen-atom-abstractions.[12]

Scheme 2



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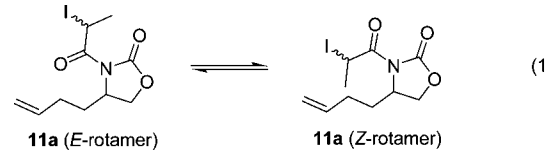
Azocan-2-ones, along with their reduction products azocanes, are important structural motifs in many biologically active natural products and medicinal agents such as shearinines C and H−J[17] and manzamine alkaloids.[18] They are also versatile intermediates in a number of areas ranging from organic synthesis to polymer chemistry. However, the efficient and general synthesis of eight-membered lactams is still a challenging task.[19] For example, the dehydration of ω-amino acids often gives low yields of azocanones.[20] The Beckmann rearrangement of ketoximes suffers from harsh reaction conditions and poor chemoselectivity.[21] The recently developed ring-closing metathesis requires the use of expensive and air-sensitive transition metal complexes.[22] The importance of azocanones urged us to study the reactivity of α-carbamoyl radicals in detail. In this paper, we report the experimental results and theoretical basis on the regio- and stereocontrol of this 8-*endo* cyclization.

Results

N-Acyloxazolidinone **11a** was first designed as the model substrate for the 8-*endo* cyclization. It could be anticipated that **11a** would exist exclusively in the *E*-conformation to avoid the steric interaction between the olefinic chain and the iodoethyl moiety in its *Z*-conformation (eq 1). On the other hand, the *Z*-conformation would predominate if the bidentate chelation between a Lewis acid and the two carbonyl groups in **11a** could be effectively formed. Such a concept[23] has been widely applied in a variety of stereoselective organic transformations, including asymmetric radical reactions developed by Sibi.[24] In our case it would allow us to direct the 8-*endo* radical cyclization to proceed via either the fixed *Z*- or the fixed *E*-conformational TS.

The cyclization of substrate **11a** without the presence of a Lewis acid was carried out. The treatment of **11a** with BEt_3 (20 mol %)/O_2 in CH_2Cl_2 (0.03 M) at room temperature (rt) for



11a (*E*-rotamer) ⇌ **11a** (*Z*-rotamer) (1)

10 min afforded a mixture of cyclized products **12a** (23%) and **13a** (27%), whose structures were unambiguously established by their X-ray diffraction experiments. The irradiation of **11a** by sunlamp in the presence of $(Bu_3Sn)_2$[16b,25] (40 mol %) resulted in a much slower reaction (rt, 12 h). However, the outcome was almost identical (24% yield of **12a** and 27% yield of **13a**). No corresponding 7-*exo* cyclization products could be detected. In a similar fashion, the reactions of substrates **11b**−**11f** bearing different alkyl groups at the α-position were also examined with BEt_3/O_2 as the initiator, and the results are summarized in Table 1. In all cases the 8-*endo* cyclization products were isolated in moderate yields, while no 7-*exo* products could be observed. All products **12** and **13** have the 3,8-*trans* configuration. The ratio of **12** to **13** increases with the increasing bulkiness of the R group.

The cyclization of substrate **11a** in the presence of a Lewis acid[26] was then examined (Table 2). With 1 equiv of $Yb(OTf)_3$ as the additive, the reaction of **11a** with BEt_3/O_2 yielded the mixture of **12a**, **13a** and the third product **14a**, all in low yields (entry 1, Table 2). The structure of **14a** was also unambiguously determined by X-ray diffraction experiment. Note that compound **14a** has the 3,8-*cis* configuration, implying that it could be generated via a different TS, which will be further discussed later. Changing the Lewis acid to $Zn(OTf)_2$ or $Mg(OTf)_2$ did not show any improvement (entries 2 and 3, Table 2). We then turned to trifluoroborane etherate for help.[12,14,27] Initially the commercially available $BF_3\cdot OEt_2$ was directly used without further purification. With the presence of 4 equiv of such kind of $BF_3\cdot OEt_2$, the reaction of **11a** gave **14a** in 31% yield, while only trace amounts of **12a** and **13a** could be detected (entry 5, Table 2). When BEt_3/O_2 was switched to $(Bu_3Sn)_2/h\nu$, the yield of **14a** was increased to 53% (entry 6, Table 2). However, the reaction was hard to repeat when freshly distilled $BF_3\cdot OEt_2$ was used (entry 7, Table 2). Such a phenomenon had previously been observed by us in the oligomerization of α-carbonyl radicals.[28] With the assumption that the aged $BF_3\cdot OEt_2$ might be contaminated by moisture, we deliberately added water into the reaction system. To our delight, when 4 equiv of freshly distilled $BF_3\cdot OEt_2$ and 0.2 equiv of water were used as the additives, the reaction of **11a** proceeded smoothly, leading to the exclusive formation of **14a** in 70% yield (entry 11, Table 2).[29]

The optimized conditions (entry 11, Table 2) were then applied to the reactions of other substrates **11b**−**11g**. We were pleased to find that, in all cases, the corresponding 8-*endo* cyclization products **14** were achieved in high yields with

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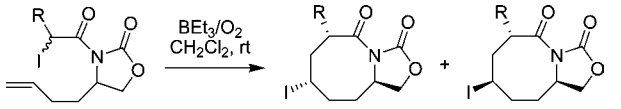
Table 1. BEt_3/O_2-Initiated Radical Cyclization of Oxazolidinones **11**

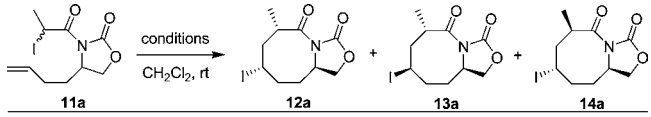


11a-f **12a-f** **13a-f**

entry[a]	substrate	R	product (yield, %)[b]	
1	**11a**	Me	**12a** (23)	**13a** (27)
2	**11b**	Et	**12b** (31)	**13b** (13)
3	**11c**	Bu	**12c** (35)	**13c** (10)
4	**11d**	C_6H_{13}	**12d** (36)	**13d** (10)
5	**11e**	*i*-Pr	**12e** (45)	**13e** (trace)
6	**11f**	*t*-Bu	**12f** (42)	**13f** (trace)

[a] Reaction conditions: **11** (0.3 mmol), BEt_3 (0.06 mmol), CH_2Cl_2 (10 mL), rt, 10 min. [b] Isolated yield based on **11**.

Table 2. Effect of Lewis Acids on Product Distribution of the Cyclization of **11a**



11a **12a** **13a** **14a**

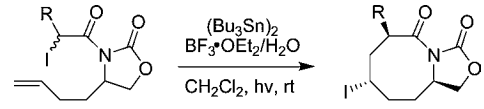
		yield (%)[b]		
entry[a]	conditions	**12a**	**13a**	**14a**
1	BEt_3 (20 mol %)/O_2, $Yb(OTf)_3$ (100 mol %), 1 h	10	11	18
2	BEt_3 (20 mol %)/O_2, $Zn(OTf)_2$ (100 mol %), 2 h	12	13	8
3	BEt_3 (20 mol %)/O_2, $Mg(OTf)_2$ (100 mol %), 5 h	11	12	0
4	BEt_3 (20 mol %)/O_2, $BF_3\cdot OEt_2$ (aged, 200 mol %), 1 h	12	13	23
5	BEt_3 (20 mol %)/O_2, $BF_3\cdot OEt_2$ (aged, 400 mol %), 1 h	trace	trace	31
6	$(Bu_3Sn)_2$ (30 mol %), $BF_3\cdot OEt_2$ (aged, 400 mol %), *hν*, 1 h	0	trace	53
7	$(Bu_3Sn)_2$ (30 mol %), $BF_3\cdot OEt_2$ (freshly distilled, 400 mol %), *hν*, 1 h	0	trace	21
8	$(Bu_3Sn)_2$ (30 mol %), $BF_3\cdot OEt_2$ (freshly distilled, 400 mol %), H_2O (400 mol %), *hν*, 1 h	0	0	58
9	$(Bu_3Sn)_2$ (30 mol %), $BF_3\cdot OEt_2$ (freshly distilled, 400 mol %), H_2O (200 mol %), *hν*, 1 h	0	0	60
10	$(Bu_3Sn)_2$ (30 mol %), $BF_3\cdot OEt_2$ (freshly distilled, 400 mol %), H_2O (40 mol %), *hν*, 1 h	0	0	67
11	$(Bu_3Sn)_2$ (30 mol %), $BF_3\cdot OEt_2$ (freshly distilled, 400 mol %), H_2O (20 mol %), *hν*, 1 h	0	0	70

[a] Reaction conditions: **11a** (0.3 mmol), CH_2Cl_2 (10 mL), additives, rt. [b] Isolated yield based on **11a**.

excellent regio- and stereoselectivity (Table 3). More importantly, the product configuration was changed from 3,8-*trans* to 3,8-*cis*. The presence of $BF_3\cdot OEt_2/H_2O$ significantly increased the efficiency and stereoselectivity of cyclization presumably by stabilizing the *Z*-rotamers of the substrates via complexation (vide infra). It should be mentioned that the substrates were prepared from racemic serine (see the Supporting Information for details). The optically pure L-serine was also utilized for the synthesis of **11a** in order to examine the diastereoselectivity of cyclization. The reaction of **11a**, thus prepared from the corresponding oxazolidinone intermediate in a 95% enantiomeric

(29) Without the use of BEt_3/O_2 or $(Bu_3Sn)_2/h\nu$, the cyclization did not proceed at all, even at refluxing temperature for a prolonged time, indicating that the reaction could not be an ionic process. Furthermore, the attempted ionic iodocarbocyclization with the deiodinated derivative of **11a** as the substrate failed to give any carbocyclization product under various conditions tested ($NaHCO_3/I_2$, LDA/I_2, BuLi/NIS, or $^tBuOCl/I_2$). For examples of ionic iodocarbocyclization, see: (a) Kitagawa, O.; Inoue, T.; Hirano, K.; Taguchi, T. *J. Org. Chem.* **1993**, *58*, 3106. (b) Kitagawa, O.; Inoue, T.; Taguchi, T. *Tetrahedron Lett.* **1992**, *33*, 2167.

Table 3. $BF_3\cdot OEt_2/H_2O$-Promoted Cyclization of Oxazolidinones **11**



11a-g **14a-g**

entry[a]	R	product	yield (%)[b]
1	Me	**14a**	70
2	Et	**14b**	82
3	Bu	**14c**	84
4	C_6H_{13}	**14d**	80
5	*i*-Pr	**14e**	83
6	*t*-Bu	**14f**	87
7	H	**14g**	73

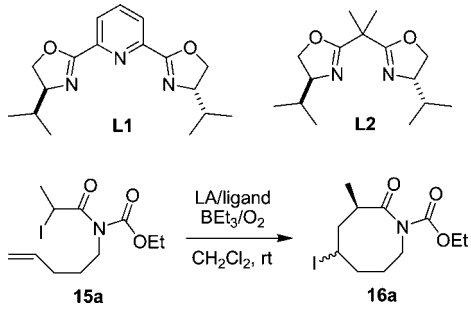
[a] Reaction conditions: **11** (0.3 mmol), $(Bu_3Sn)_2$ (0.09 mmol), $BF_3\cdot OEt_2$ (0.12 mmol), H_2O (0.06 mmol), CH_2Cl_2 (10 mL), rt, *hν*, 1 h. [b] Isolated yield based on **11**.

excess (ee), afforded the cyclized product **14a** with a 94% ee, indicating that the absolute configuration of C-8 was nicely retained.

The above reactions dealt with *N*-acyloxazolidinone substrates that have relatively rigid conformations. To gain further understanding on the behavior of 8-*endo* cyclization of α-carbamoyl radicals, we set out to study the cyclization of *N*-ethoxycarbonyl-substituted substrate **15a**, which is structurally similar to oxazolidinone **11a** but conformationally more flexible. The direct treatment of **15a** with BEt_3/O_2 in CH_2Cl_2 at rt yielded the eight-membered lactam **16a** in 56% yield as the mixture of two stereoisomers in about 2:1 ratio. The above optimized conditions ($BF_3\cdot OEt_2/H_2O$, $(Bu_3Sn)_2$, *hν*) were then applied to the reaction of **15a**. To our disappointment, no improvement could be achieved either on the product yield or on the stereoselectivity. This prompted us to reoptimize the reaction conditions under Lewis acid catalysis (Table 4). The presence of $Yb(OTf)_3$ or $Zn(OTf)_2$ showed no effect (entries 3 and 4, Table 4), presumably because of their poor solubility in CH_2Cl_2.[30] To increase the solubility, a ligand was introduced. Two types of ligands of wide applications, pyridine-2,6-bis(oxazoline) **L1**[31] and bis(oxazoline) **L2**,[32] were chosen. After the screening of a few combinations (entries 5−10, Table 4), we were pleased to find that, with the aid of 1.5 equiv of $Mg(ClO_4)_2$ and 1.5 equiv of **L2**, the reaction of **15a** afforded the 8-*endo* cyclization product **16a** in 92% yield with the *trans*/*cis* ratio of about 8 to 1 (entry 10, Table 4). The *trans* configuration of the major isomer was determined by the relevant proton coupling constants as well as 2D NMR experiments (see Supporting Information for details). The ee of the *trans*-isomer was measured to be 9%. Nevertheless, we continued to use the chiral ligand **L2** in the control of stereoselectivity because of its easy availability.[33,34] Lowering the amounts of $Mg(ClO_4)_2$/**L2** or the reaction temperature resulted in the decrease of both the product yield and the stereoselectivity (entries 11 and 12, Table 4). The reaction had a better performance in CH_2Cl_2 than in toluene (entry 13, Table 4).

(30) For a similar discussion, see: Dakternieks, D.; Perchyonok, V. T.; Schiesser, C. H. *Tetrahedron: Asymmetry* **2003**, *14*, 3057.
(31) Desimoni, G.; Faita, G.; Quadrelli, P. *Chem. Rev.* **2003**, *103*, 3119.
(32) (a) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1. (b) Jorgensen, K. A.; Johannsen, M.; Yao, S.; Audrain, H.; Thornauge, J. *Acc. Chem. Res.* **1999**, *32*, 605.

Table 4. Optimization of Reaction Conditions for Amide **15a**



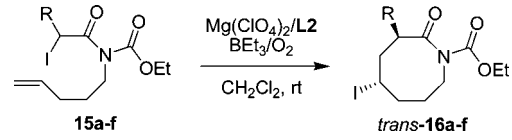
entry[a]	LA (mol %)	ligand (mol %)	yield (%)[b]	*trans*:*cis*[c]
1	none	none	56	66:34
2	$BF_3 \cdot OEt_2$ (400)	none	39	50:50
3	$Yb(OTf)_3$ (100)	none	55	66:34
4	$Zn(OTf)_2$ (100)	none	53	66:34
5	$Yb(OTf)_3$ (100)	**L1** (100)	52	73:27
6	$Yb(OTf)_3$ (300)	**L1** (300)	85	76:24
7	$Cu(OTf)_2$ (300)	**L1** (300)	*f*	
8	$Cu(OTf)_2$ (300)	**L2** (300)	*f*	
9	$Mg(ClO_4)_2$ (300)	**L2** (300)	69	88:12
10	**$Mg(ClO_4)_2$ (150)**	**L2 (150)**	**92**	**89:11**
11	$Mg(ClO_4)_2$ (30)	**L2** (30)	48	50:50
12[d]	$Mg(ClO_4)_2$ (150)	**L2** (150)	74	84:16
13[e]	$Mg(ClO_4)_2$ (150)	**L2** (150)	65	74:26
14	$Mg(ClO_4)_2$ (200)	**L1** (200)	38	81:19

[a] Reaction conditions: **15a** (0.3 mmol), BEt_3 (0.09 mmol), LA/ligand, CH_2Cl_2 (10 mL), O_2 (5 mL), rt, 1 h. [b] Isolated yield based on **15a**. [c] Determined by ^1H NMR (300 MHz). [d] The reaction was run at 0 °C. [e] Toluene was used as the solvent. [f] A complex mixture was generated from which no pure product **16a** could be isolated.

The reoptimized conditions (entry 10, Table 4) were then applied to the cyclization reactions of **15b**−**15f**, and the results are summarized in Table 5. We were delighted to find that, in all the cases, the 8-*endo* cyclization products were obtained in high yields, while no corresponding 7-*exo* cyclization products could be detected. The increase of the bulkiness of the R group in **15** further increased the stereoselectivty (*trans*:*cis* > 20:1). Compared to the cyclization of NH-amide **4** (Scheme 2),[14] the efficiency of lactam formation was dramatically increased by the introduction of the *N*-ethoxycarbonyl group. It is worth mentioning that the reoptimized conditions also allowed the cyclization of oxazolidinone **11a** to proceed smoothly to give the expected product **14a** in 72% yield, implying that $BF_3 \cdot OEt_2/H_2O$ had a role similar to that of $Mg(ClO_4)_2$/**L2**.

It should be pointed out that halogen-atom-transfer radical cyclization in an *endo* mode usually has a poor stereoselectivity.[12] To learn more on this, compound **17** as the bromo-analogue of **15a** was prepared and subjected to the above

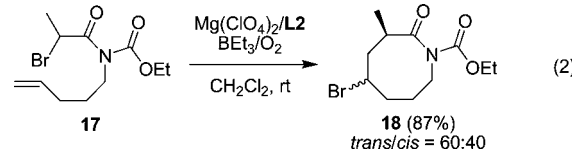
Table 5. 8-*Endo* Cyclization of *N*-Ethoxycarbonyl-Substituted Iodoamides **15**



entry[a]	**14**	R	product	yield (%)[b]
1	**15a**	Me	**16a**[c]	92
2	**15b**	Et	*trans*-**16b**[d]	87
3	**15c**	Bu	*trans*-**16c**[d]	80
4	**15d**	C_6H_{13}	*trans*-**16d**[d]	83
5	**15e**	*i*-Pr	*trans*-**16e**[d]	79
6	**15f**	*t*-Bu	*trans*-**16f**[d]	77

[a] Reaction conditions: **15** (0.3 mmol), $Mg(ClO_4)_2$ (0.45 mmol), **L2** (0.45 mmol), BEt_3 (0.09 mmol), O_2 (5 mL), CH_2Cl_2 (10 mL), rt, 1 h. [b] Isolated yield based on **15**. [c] *Trans*:*cis* = 89:11. [d] The *cis* isomer was not observed by ^1H NMR (300 MHz).

reoptimized conditions. The bromine-atom-transfer radical cyclization product **18** was achieved in a good efficiency (eq 2).[35] However, the stereoselectivity dropped to 2:1. This implies that the fast trapping of the cyclized radicals is necessary in order to achieve high stereoselectivity, which will be further analyzed later in the theoretical calculation section.



The successful results in Tables 3 and 5 urged us to investigate the cyclization of *N*-aryl-substituted substrates analogous to **8**. Iodoamide **19a** as the *N*-ethoxycarbonyl-substituted derivative of **8** was then synthesized as the model substrate. The direct treatment of **19a** with BEt_3/O_2 in CH_2Cl_2 at rt gave the 8-*endo* cyclization product **20a** in 60% as the 1:9 mixture of *trans*- and *cis*-isomers, the latter being the major isomer. With the use of $Mg(ClO_4)_2$/**L2** as the Lewis acid, **20a** was obtained in 74% yield with a ratio of *cis*/*trans* over 10:1. When the combination of $BF_3 \cdot OEt_2$ and H_2O as indicated in Table 3 was employed, **20a** was achieved in 80% yield as a single stereoisomer, whose structure was also confirmed by its X-ray diffraction experiment. Thus, without further optimization of reaction conditions, a number of *N*-arylamides **19b**−**19f** were prepared and subjected to treatment with BEt_3/O_2 under the promotion of $BF_3 \cdot OEt_2/H_2O$ (Table 6). The corresponding benzazocanones **20** were obtained exclusively in high yields. In sharp contrast to the cyclization of NH-amide **8** (Scheme 2),[14] excellent regio- and stereoselectivity were now observed. Also note that the products **20** have the 3,5-*cis* configuration rather than the opposite in lactams **14** and **16**.

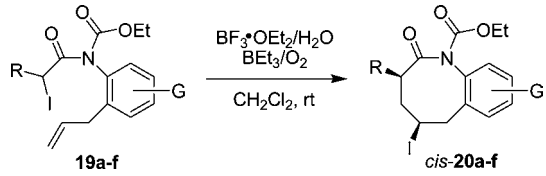
Encouraged by the above excellent control of stereoselectivity, we moved one step further to study the chemistry of iodoamide **21a** with two methyl substituents, one α to the amide carbonyl and the other α to the nitrogen. The optimized conditions (BEt_3/O_2, $Mg(ClO_4)_2$/**L2**) for the cyclization of substrates **15** were directly applied to the reaction of **21a**, yielding the cyclized products (83% yield) as the mixture of two isomers in about a

(33) For selected examples of enantioselective intermolecular radical reactions, see: (a) Sibi, M. P.; Yang, Y.-H.; Lee, S. *Org. Lett.* **2008**, *10*, 5349. (b) Hein, J. E.; Zimmerman, M. P.; Sibi, M. P.; Hultin, P. G. *Org. Lett.* **2005**, *7*, 2755. (c) Sibi, M. P.; Petrovic, G.; Zimmerman, J. *J. Am. Chem. Soc.* **2005**, *127*, 2390. (d) Sibi, M. P.; Rheault, T. R.; Chandramouli, S. V.; Jasperse, C. P. *J. Am. Chem. Soc.* **2002**, *124*, 2924. (e) Sibi, M. P.; Chen, J. *J. Am. Chem. Soc.* **2001**, *123*, 9472. (f) Sibi, M. P.; Ji, J.; Wu, J. H.; Gurtler, S.; Porter, N. A. *J. Am. Chem. Soc.* **1996**, *118*, 9200.

(34) Successful examples of enantioselective radical cyclization reactions are rare and deal solely with the 5-*exo* mode of cyclization. See: (a) Miyabe, H.; Asada, R.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 5863. (b) Yang, D.; Gu, S.; Yan, Y.-L.; Zhu, N.-Y.; Cheung, K.-K. *J. Am. Chem. Soc.* **2001**, *123*, 8612. (c) Yang, D.; Gu, S.; Yan, Y.-L.; Zhao, H.-W.; Zhu, N.-Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 3014. (d) Yang, D.; Zheng, B.-F.; Gao, Q.; Gu, S.; Zhu, N.-Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 255.

(35) For selected bromine-atom-transfer radical reactions, see: (a) Mero, C. L.; Porter, N. A. *J. Am. Chem. Soc.* **1999**, *121*, 5155. (b) Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K.; Omoto, K.; Fujimoto, H. *J. Org. Chem.* **2001**, *66*, 7776.

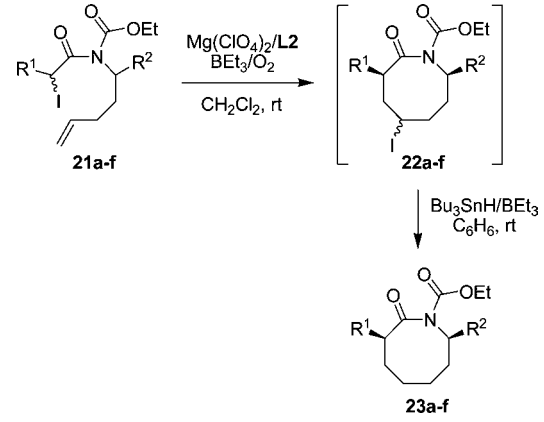
Table 6. 8-*Endo* Cyclization of *N*-Arylamides **19**



entry[a]	19	R	G	product	yield (%)[b]
1	**19a**	Me	H	*cis*-**20a**	80
2	**19b**	Et	H	*cis*-**20b**	77
3	**19c**	*t*-Bu	H	*cis*-**20c**	73
4	**19d**	Me	6-Me	*cis*-**20d**	72
5	**19e**	Me	6-OMe	*cis*-**20e**	69
6	**19f**	Me	4-Cl	*cis*-**20f**	79

[a] Reaction conditions: **19** (0.3 mmol), $BF_3 \cdot OEt_2$ (0.12 mmol), H_2O (0.06 mmol), BEt_3 (0.09 mmol), O_2 (5 mL), CH_2Cl_2 (10 mL), rt, 1 h. [b] Isolated yield based on **19**.

Table 7. Cyclization−Reduction of Iodoamides **21**



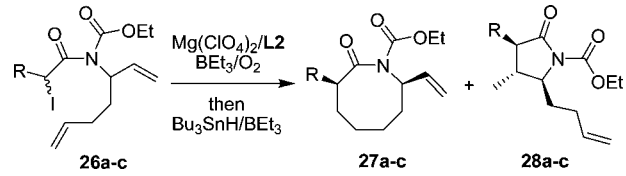
entry[a]	21	R	G	23	yield (%)[b]
1	**21a**	Me	Me	**23a**	77
2	**21b**	Et	Me	**23b**	76
3	**21c**	Bu	Me	**23c**	80
4	**21d**	*i*-Pr	Me	**23d**	74
5	**21e**	Bu	Et	**23e**	79
6	**21f**	*i*-Pr	C_5H_{11}	**23f**	74

[a] Reaction conditions: (1) **21** (0.3 mmol), $Mg(ClO_4)_2$ (0.45 mmol), **L2** (0.45 mmol), BEt_3 (0.09 mmol), O_2 (5 mL), CH_2Cl_2 (10 mL), rt, 4 h; (2) Bu_3SnH (0.6 mmol), BEt_3 (0.6 mmol), O_2 (3 × 10 mL), C_6H_6 (5 mL), rt, 10 min. [b] Isolated yield based on **21**.

1:1 ratio. The two isomers were not only inseparable by column chromatography on silica gel but also not very stable. To characterize, the crude products were reduced by excess (2 equiv) Bu_3SnH/BEt_3 in benzene at rt. The reduced product **23a** was thus isolated as a single stereoisomer in 77% yield based on the starting material **21a**. The stereochemistry of **23a** was clearly determined by its NOESY experiments, which showed a strong NOE between the two protons at C-3 and C-8 positions. This indicated that the iodine-atom-transfer cyclization products in the first step were **22a**. Although the stereochemical control in the I-abstraction was poor, the excellent control of the 3,8-*cis* stereochemistry was achieved in the 8-*endo* cyclization.

To test the generality of this stereoselective 8-*endo* cyclization, the above two-step sequence was extended to the reactions of radical precursors **21b**−**21f** (Table 7). In all cases the corresponding products **23b**−**23f** were generated in high yields as single stereoisomers. Note that the same 3,8-*cis* configuration was also observed in the cyclized products **14**, indicating the

Table 8. Competition between 8-*Endo* and 5-*Exo* Cyclizations

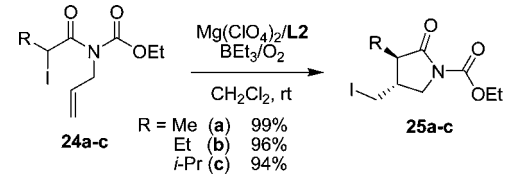


		product/yield (%)[b]		
entry[a]	R	8-*endo*	5-*exo*[c]	**28**
1	Me	**27a** (43)	38	**28a** (21)
2	Et	**27b** (28)	45	**28b** (31)
3	*i*-Pr	**27c** (trace)	66	**28c** (50)

[a] Reaction conditions: (1) **26** (0.3 mmol), $Mg(ClO_4)_2$ (0.45 mmol), **L2** (0.45 mmol), BEt_3 (0.09 mmol), O_2 (5 mL), CH_2Cl_2 (10 mL), rt, 4 h; (2) Bu_3SnH (0.6 mmol), BEt_3 (0.6 mmol), O_2 (3 × 10 mL), C_6H_6 (5 mL), rt, 10 min. [b] Isolated yield based on **26**. [c] The combined yield of pyrrolidinones.

generality of this stereoselectivity in the 8-*endo* cyclization of α-carbamoyl radicals with bidentate chelation.

The bidentate chelation played a crucial role in the above 8-*endo* cyclization. The regio- and stereoselectivity of cyclization were dramatically increased. In the meantime, the efficiency of cyclization was also significantly improved. Such a strategy could also be extended to the control of other modes of cyclization of α-carbamoyl radicals. As an example, the 5-*exo* cyclization[36] of *N*-ethoxycarbonyl-substituted iodoamides **24a**−**24c** under the above optimized conditions with $Mg(ClO_4)_2$/**L2** led to the exclusive formation of **25a**−**25c** as single stereoisomers in almost quantitative yields (eq 3). Compared to literature reports,[36] a much better control of stereoselectivity was achieved under milder conditions.

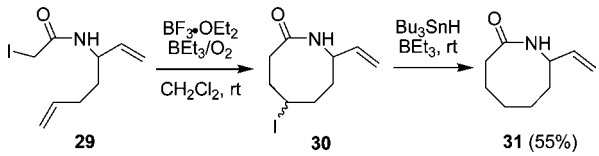


(3)

Both the 5-*exo* and the 8-*endo* cyclization of *N*-ethoxycarbonyl-substituted α-carbamoyl radicals exhibited a high efficiency. This aroused our interest in the direct competition between these two modes of cyclization. Substrates **26a**−**26c** were thus synthesized for this purpose. The cyclization−reduction sequence outlined in Table 7 was carried out for **26a**−**26c**, and the results are depicted in Table 8. Both azocanones and pyrrolidinones were obtained. The 8-*endo* cyclization products **27** were isolated as single stereoisomers. The 5-*exo* cyclization product pyrrolidinones consisted of at least three isomers with **28** as the major isomers as indicated by LC−MS analysis. Compounds **28a**−**c** were then isolated by preparative HPLC, and their stereochemistry was readily determined by the relevant proton coupling constants (see Supporting Information for details). Both the combined yields of pyrrolidinones and the isolated yields of **28a**−**c** were listed in Table 8. In the reaction of **26a**, azocanone **27a** was achieved in 43% yield while the combined yield of pyrrolidinones was only 38%, indicating that the 8-*endo* cyclization was even slightly preferred over the corresponding 5-*exo* cyclization. With the increase of bulkiness

(36) For selected examples, see: (a) Ikeda, M.; Teranishi, H.; Nozaki, K.; Ishibashi, H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1691. (b) Cao, L.; Li, C. *Tetrahedron Lett.* **2008**, *49*, 7380.

Scheme 3

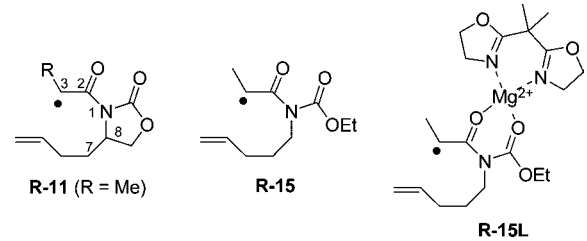


of the R group in **26**, the yield of 8-*endo* cyclization product decreased. Based on this trend, it could be anticipated that the 8-*endo* cyclization would predominate if the R group in **26** was H. Unfortunately, our various attempts to synthesize this substrate all failed; only deiodinated compound could be isolated. This phenomenon might be analyzed by the instability of **26** (R = H) due to the possible intramolecular nucleophilic substitution.

As a comparison, the radical cyclization of amide **29** without *N*-ethoxycarbonyl-substitution was also carried out (Scheme 3). With the promotion of $BF_3 \cdot OEt_2$,[14] the BEt_3/O_2-initiated reaction of **29** proceeded smoothly at rt. We were pleased to find that the 8-*endo* cyclization product **30** was achieved exclusively while no corresponding 5-*exo* cyclization product could be detected. Compound **30** existed as the mixture of two stereoisomers in about 1:1 ratio determined by ^{1}H NMR. It was then reduced with Bu_3SnH/BEt_3 to azocanone **31** (55% yield based on the starting substrate **29**) and unambiguously characterized.

Calculations and Discussion

The above results have clearly demonstrated that efficient and stereoselective formation of azocanones can be achieved via the cyclization of α-carbamoyl radicals. The difference between α-carbamoyl radicals and α-ester radicals in 8-*endo* cyclization is also evident. While both processes are efficient and highly regioselective, the cyclization of α-ester radicals suffers from the poor stereoselectivity. On the other hand, an excellent control of stereoselectivity could be achieved in the cyclization of α-carbamoyl radicals. Furthermore, the Lewis acid chelation not only significantly improves the efficiency and stereoselectivity of cyclization, but also changes the product stereochemistry from 3,8-*trans* to 3,8-*cis*. To gain more insight into the unique reactivity of *N*-(4-pentenyl)-substituted α-carbamoyl radicals, we turn to density functional calculations for help, which have been demonstrated to be a fairly accurate tool in the study of radical reactions.[37] All calculations were carried out with the Gaussian 03 program[38] using the B3LYP functional and the 6-31G* basis sets for all the elements (including Mg[39]). The transition state structures and energies were fully optimized. Once convergence is reached, the harmonic vibration frequencies were calculated at this point to confirm the geometry obtained to be a true first-order saddle point. The zero-point vibrational energy and thermal corrections were also obtained at the UB3LYP/6-31G* level, from which the activation free energies ($\Delta G^{\ddagger}$) of cyclization were calculated. In some cases, calculations at UBHandHLYP/6-31G* level were also performed to confirm the relative accuracy of the UB3LYP method.[40]



The cyclization of radical **R-11** derived from substrate **11a** was first computed. The calculated activation energies and the corresponding computed TS structures at UB3LYP/6-31G* level are shown in Figure 1. The calculations at UBHandHLYP/6-31G* level were also performed, which showed an excellent consistency with the UB3LYP method (see Supporting Information for details). The 8-*endo* cyclization may proceed via two possible pathways, the *E*-conformational TS (**TS-11-8E**) or the *Z*-conformational TS (**TS-11-8Z1** or **TS-11-Z2**). Similarly, the 7-*exo* cyclization also has two possible routes, via **TS-11-7E** or **TS-11-7Z**. Of all the five structures, **TS-11-8E** is at least 6 kcal/mol lower in energy than any other structure. This strongly suggests that only the 8-*endo* cyclization via the *E*-conformational TS is possible for **R-11**. The product configuration via **TS-11-8E** is 3,8-*trans*, consistent with the experimental observations in Table 1. The relatively high activation energy (13 kcal/mol) also accounts for the moderate efficiency of cyclization of **11** in the absence of a Lewis acid.

With the presence of a Lewis acid able to form bidentate chelation with the radical precursor, it is expected that only the *Z*-conformational TS are involved in the cyclization. As either **TS-11-8Z1** or **TS-11-8Z2** is at least 3 kcal/mol lower in energy than **TS-11-7Z**, the 8-*endo* cyclization should be overwhelmingly predominant, if we assume that the Lewis acid lowers the activation energies in approximately the same extent. Both **TS-11-8Z1** and **TS-11-8Z2** lead to the cyclized product in the 3,8-*cis* configuration, consistent with the experimental observations in Table 2. Thus, the *E*-conformational TSs generate lactams **12** and **13**, while the *Z*-conformational TSs produce lactams **14**. Since $BF_3 \cdot OEt_2/H_2O$ is not a good model for theoretical calculations, we will discuss the effect of Lewis acids later with $Mg(ClO_4)_2$/**L2** as the model.

The preference of 8-*endo* cyclization of **R-11**, with or without the promotion of Lewis acids, can also be analyzed on the basis of the computed TS structures (Figure 1). The C(3)−N(2)−C(1)−C(8) dihedral angle, which is 178° in the starting radical **R-11**, is 147° in **TS-11-8E** but 123° in **TS-11-7E**. The severe conformational distortion of the amide plane in the latter case reveals that the *N*-pentenyl chain is too *short* for 7-*exo* cyclization via the *E*-conformation. With regard to the *Z*-conformers, there is not much difference in the C(3)−N(2)−C(1)−C(8) dihedral angles. However, **TS-11-7Z** exists in a boat−boat-like conformation (the amide boat and the C(5)−C(6)−C(7)−C(8) boat) with a N(1)−C(8)−C(7)−C(6) dihedral angle of 41°. This

(37) For review articles on the use of calculations in radical reactions, see: (a) Eksterowicz, J. E.; Houk, K. N. *Chem. Rev.* **1993**, *93*, 2439. (b) Schiesser, C. H.; Skidmore, M. A. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 1, p 337.

(38) Frisch, M. J. *Gaussian 03, revision C.02*; Gaussian Inc.: Wallingford, CT, 2004. See Supporting Information for the full reference.

(39) For selected examples, see: (a) Ruan, C.; Rodgers, M. T. *J. Am. Chem. Soc.* **2009**, *131*, 10918. (b) Kannappan, B.; Gready, J. E. *J. Am. Chem. Soc.* **2008**, *130*, 15063.

(40) For selected examples, see: (a) Kyne, S. H.; Schiesser, C. H.; Matsubara, H. *J. Org. Chem.* **2008**, *73*, 427. (b) Schiesser, C. H.; Matsubara, H.; Ritsner, I.; Wille, U. *Chem. Commun.* **2006**, 1067. (c) Matsubara, H.; Falzon, C. T.; Ryu, I.; Schiesser, C. H. *Org. Biomol. Chem.* **2006**, *4*, 1920. (d) Lingwood, M.; Hammond, J. R.; Hrovat, D. A.; Mayer, J. M.; Borden, W. T. *J. Chem. Theory Comput.* **2006**, *2*, 740. (e) Morihovitis, T.; Schiesser, C. H.; Skidmore, M. A. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2041.

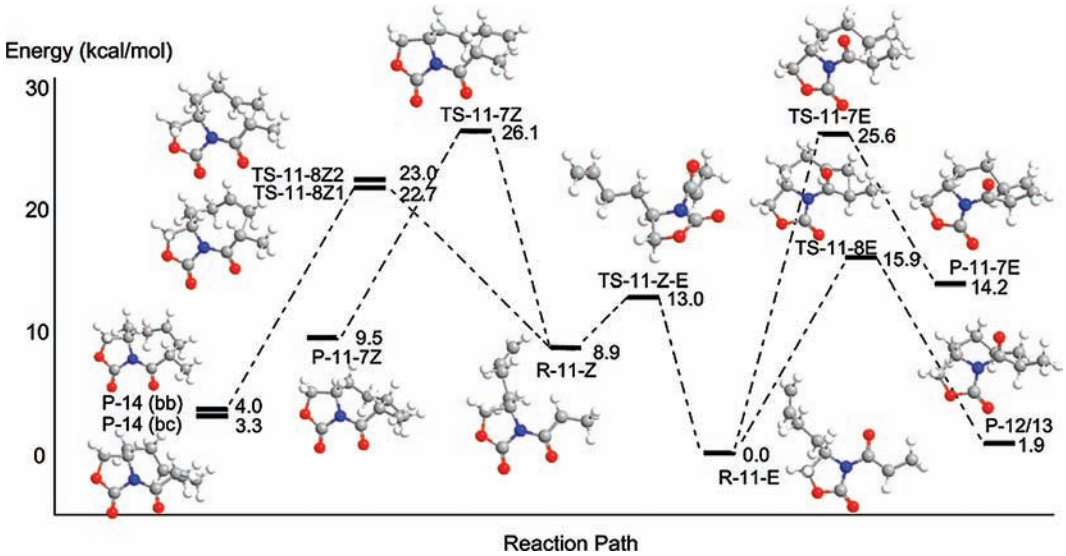


Figure 1. Computed (UB3LYP/6-31G*) 8-*endo* versus 7-*exo* cyclization of **R-11**.

Table 9. Calculated (UB3LYP/6-31G*) Activation Free Energies of 7-*Exo* versus 8-*Endo* Cyclization

	$\Delta G^{\ddagger}$ (kcal/mol)			
radical	8-*endo* (*E*)	8-*endo* (*Z*)	7-*exo* (*E*)	7-*exo* (*Z*)
R-15	14.2	19.3[a] (19.9)[b]	23.2	23.0
R-15 L		7.1[a] (7.3)[b]		11.4

[a] Boat−boat conformational TS. [b] Boat−chair conformational TS.

causes the structure rather congested as evidenced by the very short distance between the C-3 proton and the C-5 proton (2.306 Å). Although **TS-11-8Z1** also has the boat−boat-like conformation, the N(1)−C(8)−C(7)−C(6) dihedral angle is much larger (53°) and the distance between the C-3 proton and the C-5 (or C-6) proton is 3.224 Å (or 2.778 Å). On the other hand, **TS-11-8Z2** possesses the boat−chair-like conformation with a N(1)−C(8)−C(7)−C(6) dihedral angle of 71°. Thus, when the cyclization proceeds via the *E*-conformational TS, the *N*-pentenyl chain is again too *short* for 7-*exo* cyclization if compared to 8-*endo* cyclization. Therefore, whether the starting radical is fixed in the *Z*-conformation or in the *E*-conformation, the 7-*exo* cyclization always suffers from more structural distortion than the corresponding 8-*endo* cyclization, thus illustrating that the 8-*endo* mode is fundamentally preferred over the 7-*exo* mode.

The calculations on the cyclization of radical **R-15** derived from substrate **15a** were then performed. The calculated activation free energies are also listed in Table 9. The activation energy pattern in the cyclization of **R-15** closely parallels to that in the cyclization of **R-11**. Meanwhile, the TS structures are also very similar to those in the cyclization of **R-11** (see Supporting Information for details).Thus, without the promotion of a Lewis acid, 8-*endo* cyclization should prevail, consistent with the experimental results (entry 1, Table 4).

Next, the reactivity of the complexed radical **R-15L**, derived from the reaction of **15a** under the promotion of $Mg(ClO_4)_2$/**L2**, was computed. To reduce the otherwise enormous amount of time required for calculations, the ligand **L2** was replaced by its simpler analogue without the two isopropyl-substitution, namely, 2,2′-(propane-2,2-diyl)bis(4,5-dihydrooxazole). The calculated activation free energies are included in Table 9. It can be clearly seen that the Lewis acid chelation lowers the activation free energy by about 12 kcal/mol in each of the three pathways, indicating that the regioselectivity pattern is not affected by the presence of a Lewis acid. The 8-*endo* cyclization now has the activation energy of ∼7 kcal/mol. The dramatic decrease of activation energy makes the cyclization a highly efficient process, consistent with the experimental results in Table 5. Furthermore, the 3,8-*cis* stereochemistry of azocanones **23a**−**f** (Table 7) can also be well explained on the basis of the computed transition structures.

We then turn to the stereochemistry of the iodine abstraction. As mentioned above, the cyclization of radical **R-11** should proceed via *E*-conformational TS without the presence of a Lewis acid. The subsequent fast I-abstraction of the cyclized radical **P-12/13** would give predominantly the corresponding products **12a** with the 3,5-*cis* configuration. However, the product azocanones **12** and **13** all exist exclusively in the *Z*-conformations both in solid states and in a solution (see Supporting Information for details). This means that **P-12/13** in *E*-conformations have to rotate to *Z*-conformations. The rotational barrier[41] is computed at the UB3LYP/6-31G* level to be 10.0 and 14.1 kcal/mol for **P-12/13** derived from **11a** (R = Me) and **11f** (R = *t*-Bu), respectively. In the meantime, the cyclized radicals undergo I-abstraction with the rate constant of 10^6−10^7 M^{-1} s^{-1}.[42] These two competing processes resulted in the poor stereoselectivity in the reaction of **11a**. On the other hand, a very good stereoselectivity in the reaction of **11f** was observed because the rotation was much slower. This analysis is in excellent agreement with the experimental results in Table 1.

In the presence of a chelating agent, the 8-*endo* cyclization proceeds via *Z*-conformational TS. As indicated above, two possible TS are involved, the boat−boat conformational TS and the boat−chair one. The fast trapping of the cyclized radicals via the boat−boat TS of slightly lower energy would lead to the 3,5-*cis* stereoselectivity, inconsistent with the experimental results in Tables 3 and 5. To understand the 3,5-*trans* stereochemistry of azocanones **14** and **16**, the cyclized radicals derived from **R-15** and **R-15L** were computed. As shown in Figure 2,

(41) For a review on the rotational barriers of amide bonds, see: Stewart, W. E.; Siddall, T. H., III *Chem. Rev.* **1970**, *70*, 517.
(42) Curran, D. P.; Bosch, E.; Kaplan, J.; Newcomb, M. *J. Org. Chem.* **1989**, *54*, 1826.

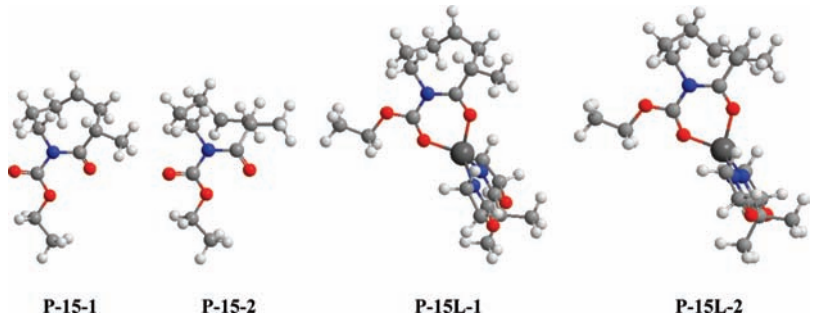


Figure 2. Computed (UB3LYP/6-31G*) structures of product radicals in the 8-*endo* cyclization of **R-15** and **R-15-MgL**.

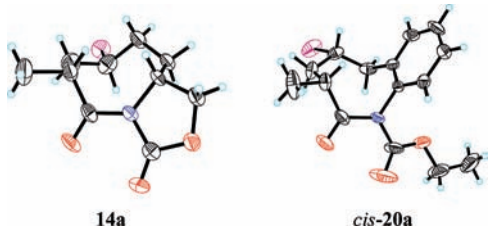
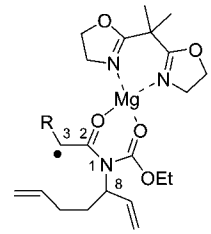


Figure 3. X-ray crystal structures of **14a** and *cis*-**20a**.

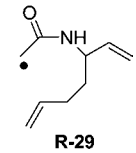
the cyclized radical via the reaction of **R-15** has two stable conformations, **P-15-1** of boat−boat conformation and **P-15-2** of boat−chair conformation. **P-15-1** is only 0.1 kcal/mol higher in energy than **P-15-2** at the UB3LYP/6-31G* level. Similarly, the cyclized radical via the reaction of **R-15L** has also two stable conformations, **P-15L-1** of boat−boat conformation and **P-15L-2** of boat−chair conformation. However, **P-15L-1** is 1.1 kcal/mol higher in energy than **P-15L-2** at the UB3LYP/6-31G* level. Thus, the fast trapping of **P-15L-1** leads to the 3,5-*trans* configuration in the final products.[43] The energy difference between **P-15L-1** and **P-15L-2** is in excellent agreement with the experimental observation in **16a** (*trans*/*cis* = 8:1). It is interesting to see that the Lewis acid chelation enlarges the energy difference between the two conformations. Such a differentiation by Lewis acid complexation can also be observed in the computation of product radicals derived from the reaction of *N*-arylamide **19a** (see Supporting Information for details). For example, in the reaction of **19a** with the 7,8-benzo-fused substitution, the boat−boat conformation is computed to be 1.1 kcal/mol lower in energy than the corresponding boat−chair conformation for the complexed product radical, thus leading to the 3,5-*cis* stereochemistry in the product **20a**. The relative stability of the two conformations is thus vulnerable to substituents. It is worth mentioning that, in the solid state, azocanone **14a** has the boat−chair conformation and benzazocanone *cis*-**20a** has the boat−boat conformation (Figure 3), consistent with the above theoretical analysis. When the iodine is replaced by a bromine atom, the stereoselectivity becomes poor as indicated in eq 2. This might be attributed to the much lower rate of Br-abstraction (10^3−10^4 M^{-1} s^{-1}) compared to I-abstraction (10^6−10^7 M^{-1} s^{-1}).[42]

The competition between 5-*exo* and 8-*endo* cyclization was also computed at the UB3LYP/6-31G* level. The complexed radicals **R-26L** (R = H, Me, or *t*-Bu) and the uncomplexed radical **R-29** were taken as the models, and the calculated activation energies are summarized in Table 10. Again, two possible TS are computed for the 8-*endo* cyclization of **R-26L** (R = Me). However, the TS of 8-*endo* cyclization of **R-26L** (R = H or *t*-Bu) are in boat−boat conformations, while the corresponding boat−chair conformations are about 2 kcal/mol higher in energy. We are delighted to find that the 8-*endo* mode of cyclization is overwhelmingly predominant over the corresponding 5-*exo* mode for radical **R-26L** (R = H). The fundamental preference of 8-*endo* cyclization can be rationalized on the basis of the transition structures. The C(3)−C(2)−N(1)−C(8) dihedral angel, which is expected to be 0° in the ideal case, is computed to be 2.5° in the TS of 8-*endo* cyclization but 31.6° in the TS of 5-*exo* cyclization. Thus, the 5-*exo* cyclization requires the severe conformational distortion in order for the α-carbamoyl radical to add to the double bond. On the other hand, the *N*-(4-pentenyl) chain is long enough to allow the addition in the 8-*endo* mode to proceed while maintaining the planarity of the amide moiety. For radicals **R-26L** (R = Me or *t*-Bu), the activation energies are increased for both pathways. However, the 5-*exo* cyclization is insensitive to the size of the R group, while the 8-*endo* cyclization slows down when the size of R increases. This different trend can also be rationalized on the basis of the TS structures in which the vinyl and the R groups point to the same direction in the TS of 8-*endo* cyclization but to different directions in the TS of 5-*exo* cyclization. Therefore, with the increasing bulkiness of the R group, the preferred mode of cyclization is reversed from 8-*endo* to 5-*exo*. This

Table 10. Calculated (UB3LYP/6-31G*) Activation Free Energies of 5-*Exo* versus 8-*Endo* Cyclization



R-26L



R-29

		$\Delta G^{\ddagger}$ (kcal/mol)	
entry	radical	8-*endo*	5-*exo*
1	**R-26L** (R = H)	1.4	4.6
2	**R-26L** (R = Me)	6.9, 6.5	6.1
3	**R-26L** (R = *t*-Bu)	9.5	6.1
4	**R-29**	10.9 (*Z*)[a], 10.9 (*E*)[b]	10.6

[a] *Z*-Conformational TS. [b] *E*-Conformational TS.

(43) The I-abstraction process was irreversible under the experimental conditions (Table 5). This was evidenced by the observation that the *cis*/*trans* ratio of product **16a** did not change when **16a** (*cis*/*trans* = 1:1) was subjected to the treatment of BEt_3/O_2 under the experimental conditions shown in Table 5.

calculated trend is in excellent qualitative agreement with our experimental results in Table 8.

For the cyclization of radical **R-29**, the activation energy of 8-*endo* cyclization is computed to be 10.9 kcal/mol via either a *Z*- or *E*-conformational TS, which is close to that of 5-*exo* cyclization. If the cyclization proceeded via *E*-conformational TS, we would expect that 5-*exo* cyclization product was also formed. The only observation of 8-*endo* cyclization product **30** illustrates that the cyclization takes place via *Z*-conformational TS only. Curran has clearly demonstrated that, once the rate of radical cyclization far exceeds that of amide bond rotation, the starting rotamer ratio of an amide radical precursor can have a significant impact on the radical cyclization.[44] As the amide substrate exists exclusively in *Z*-conformations and the rotation barrier of the amide bond in the substrate radical (18.8 kcal/mol at UB3LYP/6-31G* level) is much higher than the activation energy of 8-*endo* cyclization, only the 8-*endo* cyclization via *Z*-conformational TS is possible under the experimental conditions, while the 5-*exo* cyclization is unlikely to happen because of its requirement of *E*-conformational TS.

Finally, the above discussion also helps to clarify the mechanism of cyclization of *N*-(4-pentenyl)iodoacetamide **4** depicted in Scheme 2. The activation free energies for 8-*endo* cyclization (rather than relative energy difference in our previous report[14]) are computed to be 13.0 kcal/mol via the *Z*-conformational TS and 13.2 kcal/mol via the *E*-conformational TS. Both activation energies are lower than the rotation barrier of the amide bond.[41] Moreover, the presence of Lewis acid $BF_3 \cdot OEt_2$ should further lower the activation energies. Thus, it is unlikely that both pathways occur for 8-*endo* cyclization at the same time in the reaction of amide **4** under mild conditions as previously proposed.[14] It is more likely that the cyclization proceeds via the *Z*-conformational TS only. The cyclized product **6** with a *Z*-conformation may undergo either the amide bond rotation (to give the stable azocanone **5** in an *E*-conformation) or the intramolecular nucleophilic substitution (to give the lactone **7**). Presumably the two processes are of comparable rates, and both products are generated.

(44) (a) Curran, D. P.; Tamine, J. *J. Org. Chem.* **1991**, *56*, 2746. (b) Curran, D. P.; DeMello, N. C. *J. Chem. Soc., Chem. Commun.* **1993**, 1314. (c) Curran, D. P.; Qi, H.; Geib, S. J.; DeMello, N. C. *J. Am. Chem. Soc.* **1994**, *116*, 3131. (d) Curran, D. P.; Liu, H. T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1377. (e) Curran, D. P.; Guthrie, D. B.; Geib, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 8437.

Conclusion

The results reported herein provide a basis for understanding the unique reactivity of α-carbamoyl radicals in 8-*endo* cyclization. The cyclization can proceed via either a *Z*- or an *E*-conformational TS. In both cases, the 8-*endo* cyclization is fundamentally preferred over the corresponding 7-*exo* cyclization. The introduction of an *N*-ester group to the radical precursors, together with the promotion of a Lewis acid, not only significantly improves the efficiency of iodine-atom-transfer radical cyclization but also pushes the α-carbamoyl radicals to cyclize via fixed *Z*-conformation TS, resulting in a high degree of stereochemical control. The competition experiments illustrate that the 8-*endo* cyclization is of comparable rates to the 5-*exo* cyclization even when the substrates are in *Z*-(s-*cis*) conformations.

The calculations offer a quantitative view on the mechanism of 8-*endo* cyclization of α-carbamoyl radicals, which will certainly allow more controlled and predictable applications of this important class of 8-*endo* cyclization of haloamides. The mechanistic study along with the conformational analyses also shed light on other modes of cyclization of α-carbamoyl radicals. Furthermore, the quantitative assessment on the effect of Lewis acids can be extrapolated to other types of radical reactions as well.

Acknowledgment. This project was supported by the National Natural Science Foundation of China (Grant Nos. 20672136, 20702060, and 20832006), by the National Basic Research Program of China (Grant No. 2010CB833206), and by the Shanghai Municipal Committee of Science and Technology (Grant No. 07XD14038). We thank Shana Zhu of the Shanghai Institute of Organic Chemistry for double-checking some of the experimental data. This paper is dedicated to Prof. You-Cheng Liu, a pioneer in physical organic chemistry in China, on the occasion of his 90th birthday.

Supporting Information Available: Full experimental procedures, compound characterizations, copies of ^{1}H and ^{13}C NMR spectra of all substrates and products, DFT calculation data, crystallographic data in CIF format, and complete ref 38. This material is available free of charge via the Internet at http://pubs.acs.org.

JA9082649