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Development of Highly Regioselective Amidyl Radical Cyclization Based on Lone Pair−Lone Pair Repulsion

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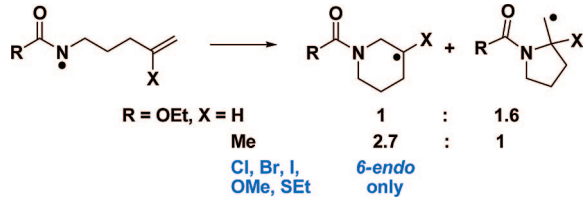

The substituent effect on the reactivity and regioselectivity of *N*-(4-pentenyl)amidyl radical cyclization was investigated. Exclusive 6-*endo* cyclization was observed for *N*-(4-pentenyl)amidyl radicals with internal vinylic heteroatom substitution (Cl, Br, I, OMe, SEt). The substituent on the carbonyl group also showed a significant influence on the reactivity of amidyl radicals, which increases in the order of Ph < Me < OEt. As a result, the photostimulated reactions of *N*-(4-halopent-4-enyl)amides and carbamates (X = Cl, Br, I) with DIB/I_2 or $Pb(OAc)_4/I_2$ led to the efficient and exclusive formation of the corresponding piperidines while those of *N*-(5-halopent-4-enyl)amides afforded the pyrrolidine products only. The halogen-substitution effect also allowed the 6-*exo* and 7-*endo* amidyl radical cyclization to proceed in a highly regioselective manner. The above experimental results, in combination with theoretical analyses, revealed that the lone pair−lone pair repulsion between the nitrogen radical and the vinylic heteroatom played an important role in controlling the regioselectivity of cyclization.

Introduction

The application of nitrogen-centered radicals in organic synthesis has gained increasing popularity in the past few years.[1] Among various nitrogen-centered radicals, amidyl radicals have received considerable attention. The highly reactive and electrophilic nature allows amidyl radicals to add to electron-rich C=C double bonds leading to the direct construction of C−N bonds.[2] In particular, the intramolecular addition provides a unique entry to N-heterocycles of various sizes,[3,4] thus offering a great potential in the synthesis of natural products such as alkaloids.[5] The oxidative entry to these transient species allows the direct use of the N−H amides, which in turn makes this radical strategy of more synthetic value. For example, Nicolaou and co-workers reported the successful *o*-iodoxybenzoic acid (IBX)-mediated 5-*exo* cyclization of unsaturated *N*-aryl amides.[3a] Studer et al. extended this methodology to the oxidative cyclization of acylated alkoxyamines.[3c]

The cyclization of amidyl radicals has two modes, to form lactams and to form cyclic amines. While most of the literature works were centered at the generation of lactams, the formation of cyclic amines received far less attention and the chemistry is not well understood. Kinetic studies[7] by Newcomb et al. revealed that the rate constant for 5-*exo* cyclization of *N*-(4-pentenyl)butanamidyl radical is 1 order of magnitude lower than

(1) For reviews, see: (a) Neale, R. S. *Synthesis* **1971**, 1. (b) Esker, J.; Newcomb, M. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: New York, 1993; Vol. 58, p 1. (c) Zard, S. Z. *Synlett* **1996**, 1148. (d) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543. (e) Stella, L. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 2, p 407.

(2) (a) Guin, J.; Much-Lichtenfeld, C.; Grimme, S.; Studer, A. *J. Am. Chem. Soc.* **2007**, *129*, 4498. (b) Kemper, J.; Studer, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 4914. (c) Walton, J. C.; Studer, A. *Acc. Chem. Res.* **2005**, *38*, 794.

(3) (a) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Barluenga, S.; Hunt, K. W.; Kranich, R.; Vega, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 2233. (b) Gagosz, F.; Moutrille, C.; Zard, S. Z. *Org. Lett.* **2002**, *4*, 2707. (c) Janza, B.; Studer, A. *J. Org. Chem.* **2005**, *70*, 6991.

(4) (a) Tang, Y.; Li, C. *Org. Lett.* **2004**, *6*, 3229. (b) Chen, Q.; Shen, M.; Tang, Y.; Li, C. *Org. Lett.* **2005**, *7*, 1625. (c) Lu, H.; Li, C. *Tetrahedron Lett.* **2005**, *46*, 5983. (d) Hu, T.; Shen, M.; Chen, Q.; Li, C. *Org. Lett.* **2006**, *8*, 2647.

(5) (a) Sharp, L. S.; Zard, S. Z. *Org. Lett.* **2006**, *8*, 831. (b) Cassayre, J.; Gagosz, F.; Zard, S. Z. *Angew. Chem., Int. Ed.* **2002**, *41*, 1783.

(6) (a) Mackiewicz, P.; Furstoss, R.; Wageel, B.; Cote, R.; Lessard, J. *J. Org. Chem.* **1978**, *43*, 3746. (b) Newcomb, M.; Esker, J. L. *J. Org. Chem.* **1993**, *58*, 4933.

(7) (a) Horner, J. H.; Musa, O. M.; Bouver, A.; Newcomb, M. *J. Am. Chem. Soc.* **1998**, *120*, 7738. (b) Martinez, E., II; Newcomb, M. *J. Org. Chem* **2006**, *71*, 557.

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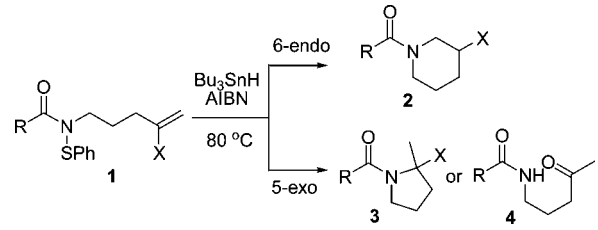
that of *N*-butyl-4-pentenamidyl radical.[7a] With regard to the implementation of cyclization reactions, an early study by Lessard and co-workers indicated that the 5-*exo* cyclization of unsaturated acetamidyl radicals is much less efficient while the 6-*exo* cyclization did not proceed at all.[6a] As a comparison, Newcomb et al. showed that the *N*-(4-pentenyl)benzamidyl radical underwent efficient 5-*exo* cyclization.[6b] However, the effect of different carbonylic substituents on the reactivity of amidyl radicals is not clear. It should also be noted that only 5-*exo* cyclization was implemented so far while cyclizations in other modes remain unknown or unsuccessful. Due to the easy removal of the acyl group of amides to provide free amines, it is certainly of interest to develop efficient and highly regioselective amidyl radical-based strategies toward the synthesis of cyclic amines.

During our investigation on the chemistry of amidyl radicals,[4] we found that the regioselectivity of 5-hexenamidyl radical cyclization could be well controlled by vinylic halogen substitution, leading to the regiospecific 6-*exo* and 7-*endo* cyclization.[4d] This remarkable halogen effect was then successfully extended to the control of regioselectivity in sulfonamidyl[8a] and primary aminyl[8b] radical cyclizations. We were motivated to find if (1) this halogen effect could be extended to the *N*-alkenylamidyl radical cyclization system and if (2) other heteroatoms could have a similar effect in controlling the regioselectivity of cyclization. Herein we report that efficient and highly regioselective 5-*exo*, 6-*endo*, 6-*exo*, and even 7-*endo* cyclization of (*N*-alkenyl)amidyl radicals could be achieved not only by vinylic halogen substitution, but also by other vinylic heteroatom (O and S) substitution. Theoretical calculations in combination with the experimental results provide us a clear understanding on the behaviors of amidyl radicals.

Results and Discussion

We first examined the vinylic substitution effect on the regioselectivity of *N*-(4-pentenyl)amidyl radical cyclization. Two typical types of amidyl radicals were employed as the models: acetamidyl and carbamidyl radicals. The *N*-phenylthio-substituted amides **1** were chosen as the radical precursors and their reactions with Bu_3SnH/AIBN were carried out in benzene at 80 °C according to Newcomb's procedure.[9] The results are summarized in Table 1. The *N*-(4-pentenyl)acetamidyl radical derived from precursor **1a** gave mainly pyrrolidine **3a** (71%) along with a small amount of piperidine **2a** (7%), indicating the predominance of 5-*exo* cyclization (entry 1, Table 1). The carbamidyl radical generated from **1b** also showed the preference of 5-*exo* cyclization (entry 2, Table 1). However, the ratio was only about 2.2 to 1, indicating the strong influence of the substituent R on the regioselectivity, which will be further discussed later. With an internal methyl substitution at the C=C bond, both the unsaturated radicals afforded the mixture of 5-*exo* and 6-*endo* cyclization products with the slight preference of 6-*endo* cyclization (entries 3 and 4, Table 1). On the other hand, switching the methyl to a chlorine atom resulted in the exclusive formation of 6-*endo* cyclization products **2e** and **2f** (entries 5 and 6, Table 1). In these two cases, the 5-*exo* cyclization products **3e** and **3f** were expected to undergo HCl elimination to give, upon workup with water, the corresponding ketones **4e** and **4f**, respectively. However, neither **3** nor **4** could be detected by the crude ^{1}H NMR. The difference between Me and Cl in controlling the regioselectivity of cyclization is remarkable. Next, we replaced the chlorine atom in **1** by an ethylthio or a methoxy group (**1g** and **1h**). Exclusive 6-*endo* cyclization was again observed and the yields of **2g** (79%) and **2h** (90%) were even higher (entries 7 and 8, Table 1).

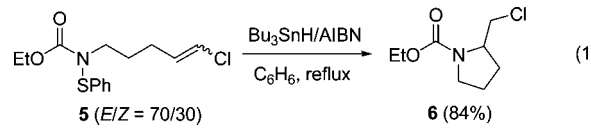
TABLE 1. Regioselectivity of Cyclization of *N*-(4-Pentenyl)amidyl Radicals



				product/yield (%)[a]	
entry	**1**	R	X	**2**	**3** or **4**
1	**1a**	Me	H	**2a** (7)	**3a** (71)
2	**1b**	OEt	H	**2b** (20)	**3b** (45)
3	**1c**	Me	Me	**2c** (47)	**3c** (28)
4	**1d**	OEt	Me	**2d** (54)	**3d** (20)
5	**1e**	Me	Cl	**2e** (60)	*b*
6	**1f**	OEt	Cl	**2f** (70)	*b*
7	**1g**	OEt	OMe	**2g** (79)	*b*
8	**1h**	OEt	SEt	**2h** (90)	*b*

[a] Isolated yield based on **1**. [b] **3** or **4** was not detected by ^{1}H NMR (300 MHz).

As a comparison, amide **5** with a terminal chlorine substitution was prepared and subjected to the same treatment as above. A clean reaction was observed and only the 5-*exo* cyclization was isolated in 84% yield (eq 1). By comparison with the result of **1b**, the terminal chlorine substitution is highly effective in directing the cyclization to proceed in a 5-*exo* mode.



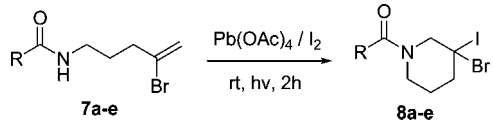
The above results demonstrated that the regioselectivities of amidyl cyclization could be well controlled by the vinylic heteroatom substitution. It is of interest to learn if other halogen atoms such as Br or I would have the same effect. However, the use of Bu_3SnH prevented the investigation because vinyl bromides or iodides are also easily reduced by Bu_3SnH. It is also highly desirable to carry out these transformations with the parent N−H amides rather than the phenylthio-substituted amides **1** as the substrates; this should be of more synthetic value. In the meantime, the effect of carbonylic substituents (R in **1**) on the reactivity of amidyl radicals has yet to be examined. Thus, we next chose the N−H amides **7** bearing an internal vinylic bromine substituent as the substrates to explore this possibility. The amides **7** were treated with $Pd(OAc)_4/I_2$[4d,8,10] upon continuous UV irradiation at room temperature and the results are listed in Table 2. The trifluoroacetamide **7a** gave no expected cyclization product while a large amount (72%) of the starting material was recovered (entry 1, Table 2). The reaction of benzamide **7b** was complicated under the experi-

(8) (a) Lu, H.; Chen, Q.; Li, C. *J. Org. Chem.* **2007**, *72*, 2564. (b) Liu, F.; Liu, K.; Yuan, X.; Li, C. *J. Org. Chem.* **2007**, *72*, 10231.

(9) Esker, J. K.; Newcomb, M. *Tetrahedron Lett.* **1993**, *34*, 6877.

(10) Barton, D. H. R.; Beckwith, A. L. J.; Goosen, A. *J. Chem. Soc.* **1965**, 181.

TABLE 2. Reactions of *N*-(4-Bromo-4-pentenyl)amides with $Pd(OAc)_4/I_2$



entry	7	R	yield (%)[a] 7	8
1	**7a**	CF_3	72	0
2	**7b**	Ph	15	20
3	**7c**	Me	0	60
4	**7d**	OEt	0	83
5	**7e**	NMe_2	0	0

[a] Isolated yield based on **7**.

TABLE 3. 5-Exo versus 6-Endo Amidyl Radical Cyclization

entry	substrate		product	yield (%)[a]
1[b]	**7d**	(X = Br)	**8d**	92
2[b]	**7f**	(X = Cl)	**8f**	86
3[b]	**7g**	(X = I)	**8g**	67
4[c]	**7h**	(R = Me)	**8h**	59
5[c]	**7i**	(R = *n*-Bu)	**8i**	42
6[c]	**7j**	(R = vinyl)	**8j**	41
7[b]	**7k**	(X = Br)[d]	**8k**	96[f]
8[b]	**7l**	(X = Cl)[e]	**8l**	93[f]
9[c]	**9**		**10**	56[g]
10[c]	**11**		**12**	71[h]

[a] Isolated yield based on the starting amide. [b] DIB/I_2 were used. [c] $Pb(OAc)_4/I_2$ were used. [d] E/Z = 85:15. [e] E/Z = 1:1. [f] Two stereoisomers in ~2:1 ratio. [g] Two stereoisomers in ~1:1 ratio. [h] Two stereoisomers in ~3:2 ratio.

mental condition and the expected 6-*endo* cyclization product **8b** was isolated in only 20% yield (entry 2, Table 2). As a comparison, the acetamide **7c** afforded the expected piperidine **8c** in 60% yield under the same experimental conditions (entry 3, Table 2). The best result was obtained in the case of ethyl carbamate **7d** in which **8d** was achieved in 83% isolated yield (entry 4, Table 2). With the use of urea **7e** as the substrate, no cyclized product could be detected and the starting material was

TABLE 4. 6-Exo versus 7-Endo Amidyl Radical Cyclization

entry	substrate		product	yield (%)[a]
1[b]	**13a**	(X = Br)	**14a**	70
2[b]	**13b**	(X = Cl)	**14b**	53
3[b]	**13c**	(X = Br)[c]	**14c**	89[e]
4[b]	**13d**	(X = Cl)[d]	**14d**	85[e]

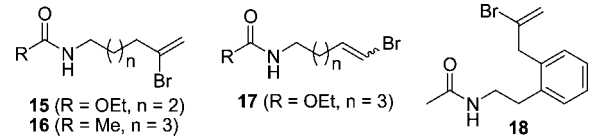
[a] Isolated yield based on **13**. [b] $Pb(OAc)_4/I_2$ were used. [c] *E/Z* = 3/1. [d] *E/Z* = 4/1. [e] Two stereoisomers in ~3:2 ratio.

all decomposed presumably because of the possible demethylation of **7e** under the oxidative conditions (entry 5, Table 2).

The results in Table 2 indicated that unsaturated acetamides and carbamates such as **7c** and **7d** could be the ideal candidates for amidyl radical cyclization reactions. Our further efforts in the optimization of reaction conditions showed that, with the use of 2 equiv of (diacetoxyiodo)benzene (DIB) and 1.5 equiv of iodine,[4d,9,11] the UV irradiation of **7d** in CH_2Cl_2 at rt resulted in a clean reaction leading to the isolation of the product **8d** in 92% yield. On the other hand, under this milder condition (DIB/I_2), the reaction of **7c** gave the cyclized product **8c** in only 22% yield. These data implied that carbamidyl radicals are more reactive than the corresponding acetamidyl radicals.[12]

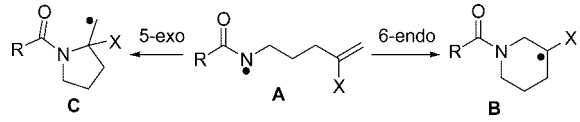
We then prepared a number of carbamates and alkanamides and subjected them to the reaction with DIB/I_2 or $Pb(OAc)_4/I_2$. The results are summarized in Table 3. The Br or I substitution showed the same effect as Cl in controlling the regioselectivity of cyclization. With internal vinylic halogen subsitution, the piperidine products were obtained while no corresponding 5-*exo* cyclization products similar to **3** or **4** could be detected (entries 1−6, Table 3). The ethyl carbamates gave higher product yields than the corresponding alkanamides (entries 2 and 4−6, Table 3). On the other hand, with terminal halogen substitution, only the 5-*exo* cyclization product pyrrolidines were isolated (entries 7 and 8, Table 3). The cyclic carbamates **9** and **11** showed similar behaviors (entries 9 and 10, Table 3).

We then extended the above cyclization reactions to the 6-*exo* versus 7-*endo* cyclization system (Table 4). The same halogen effect was observed. The *gem*-dimethyl-substitution in **13a−d** was designed to avoid the possible intramolecular 1,5-H abstraction of carbamidyl radicals. As a comparison, substrate **15** without dimethyl substitution failed to give the expected cyclization product. Our attempt to further extend the above strategy to the cyclization in a 7-*exo* or 8-*endo* mode with the use of amides **15−18** as substrates was unsuccessful.



The above results clearly demonstrated that efficient and higly regioselective cyclization could be achieved for unsaturated

TABLE 5. Calculated (UB3LYP/6-31G*) Activation Energies for the Cyclization of Radicals A



entry	R	X	$\Delta G^{\ddagger}$(5-exo)[a]	$\Delta G^{\ddagger}$(6-endo)[a]
1	CF_3	Br	8.3	5.6
2	OEt	Br	10.6	7.0
3	Me	Br	11.1	9.2
4	n-Bu	Br	11.0	8.7
5	i-Pr	Br	11.0	9.4
6	Ph	Br	12.0	10.3
7	NMe_2	Br	13.6	12.7
8	Me	H	8.0	10.2
9	Me	Me	9.0	8.4
10	Me	Cl	12.0	9.7
11	OEt	H	7.3	8.6
12	OEt	Me	7.8	7.1
13	OEt	Cl	11.2	7.7
14	OEt	I	11.1	7.6
15	OEt	OMe	8.5	7.1
16	OEt	SEt	11.4	6.1

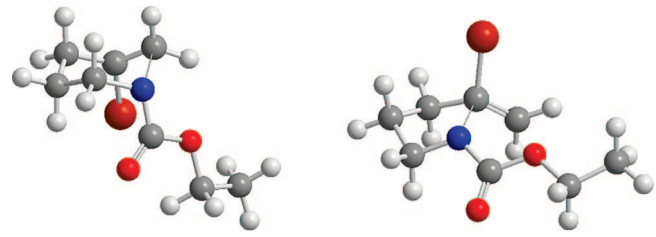
[a] In kcal/mol.

TABLE 6. Computed (UB3LYP/6-31G*) Mulliken Charges (MC) on the Nitrogen in Radicals A (X = Br)

	R =						
	CF_3	OEt	Me	*n*-Bu	*i*-Pr	Ph	NMe_2
MC	−0.313	−0.329	−0.322	−0.333	−0.337	−0.359	−0.381

acetamidyl and carbamidyl radicals. To gain more insight into the reactivity of *N*-(4-pentenyl)amidyl 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.[13,14] The transition state structures and energies were fully optimized at the UB3LYP/6-31G* level. 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. The computed activation free energies ($\Delta G^{\ddagger}$) for 5-*exo* and 6-*endo* cyclization are summarized in Table 5. The calculated Mulliken charges on the nitrogen atom of amidyl radicals **A** (X = Br) are listed in Table 6 (see also the Supporting Information for details).

First we focus on the influence of carbonylic substituents R on the reactivity of amidyl radicals. The calculated activation energies for 6-*endo* cyclization of radicals **A** (X = Br) increases in the order of CF_3 < OEt < Me ≈ *n*-Bu ≈ *i*-Pr < Ph < NMe_2, ranging from 5.6 to 12.7 kcal/mol (entries 1−7, Table 5). A similar trend is also seen for the corresponding 5-*exo* cyclization. This remarkable substituent effect can be well interpreted based on electronic and steric effects. In terms of electronic effect, the computed Mulliken charges on the nitrogen atom of amidyl radicals **A** (X = Br) are summarized in Table 6. The lowest Mulliken charge is observed in the case of R = CF_3, while the highest one is observed for R = NMe_2. The changes in the Mulliken charges closely parallel the changes in the activation energies for cyclization, indicating the dominance of the electronic effect on the reactivity of amidyl radicals. Thus, the more electrophilic the amidyl radicals, the more reactive toward the electron-rich C=C double bond. The only difference is that the Mulliken charges are about the same for carbamidyl and alkanamidyl radicals while the activation energies for 6-*endo* cyclization show an approximately 2 kcal/mol difference. This can be analyzed via steric effect according to the computed transition state structures for cyclization. The transition states for 6-*endo* cyclization, as exemplified by structure **19** (R = OEt, X = Br), are in a chair conformation with both the carbonyl and the X groups at the axial positions. Thus, the bulkiness of R becomes an important factor. With the ethyl group swinging away to avoid the steric congestion and the ether oxygen smaller in size than Me, the ethoxy group causes, in fact, less steric hindrance than a methyl group. As a result, the activation energy for 6-*endo* cyclization of carbamidyl radicals is lower than that of acetamidyl radicals. The transition states for 5-*exo* cyclization, as exemplified by structure **20** (R = OEt, X = Br), are in an envelop conformation. With the carbonyl group at the equatorial position in **20**, the steric effect of R is now less obvious. Note that the calculated energies of 5-*exo* cyclization are about the same for both carbamidyl and acetamidyl radicals (entries 2−5, Table 5).



19 **20**

The above calculated data are in good agreement with the experimental results shown in Table 2 except for the case of CF_3. While theoretical calculations point out that trifluoroacetamidyl radicals are the most reactive, no expected product could be isolated in the reaction of trifluoroacetamide **7a**. A possible explanation for this inconsistency is that, because of the powerful electron-withdrawing nature of CF_3, the amide nitrogen is much less nucleophilic and the oxidative generation of the corresponding N−I intermediate as the radical precursor did not occur at all.

We next turn our attention to the control of regioselectivity. For *N*-(4-pentenyl)acetamidyl radical **A** (R = Me, X = H), the activation energy difference between 5-*exo* and 6-*endo* cyclization is computed to be 2.2 kcal/mol in favor of 5-*exo* cyclization (entry 8, Table 5). With an internal methyl substitution (X = Me), the energy difference is lowered to 0.6 kcal/mol (entry 9, Table 5). However, switching the methyl to a chlorine atom resulted in a difference of 2.3 kcal/mol in the activation energy,

(11) Concepcion, J. I.; Francisco, C. G.; Hernandez, R.; Salazar, J. A.; Suarez, E. *Tetrahedron Lett.* **1984**, *25*, 1953.

(12) It should be noted that the ionic iodocyclization via a 5-*exo* manner prevailed when the reactions of **7** with $Pb(OAc)_4/I_2$ or DIB/I_2 were performed in the dark. For example, the treatment of **7b** with DIB/I_2 in the dark at rt for 2 h afforded *N*-(5-iodo-4-oxopentyl)benzamide in 48% yield. See also ref 8a.

(13) For review articles on 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.

(14) (a) Chen, Q.; Li, C. *Organometallics* **2007**, *26*, 223. (b) Itoh, Y.; Houk, K. N.; Mikami, K. *J. Org. Chem.* **2006**, *71*, 8918. (c) O'Neil, L. L.; Wiest, O. *J. Org. Chem.* **2006**, *71*, 8926. (d) Hartung, J.; Daniel, K.; Rummey, C.; Bringmann, G. *Org. Biomol. Chem.* **2006**, *4*, 4089. (e) Lin, H.; Chen, Q.; Cao, L.; Yang, L.; Wu, Y.-D.; Li, C. *J. Org. Chem.* **2006**, *71*, 3328. (f) Liu, L.; Chen, Q.; Wu, Y.-D.; Li, C. *J. Org. Chem.* **2005**, *70*, 1539. (g) Speybroeck, V. V.; De Kimpe, N.; Waroquier, M. J. *Org. Chem.* **2005**, *70*, 3674. (h) References 4b and 4d.

indicating the predominance of 6-*endo* cyclization (entry 10, Table 5). The effect of Cl substitution is even more obvious in the cases of carbamidyl radicals (entries 11−13, Table 5). An activation energy difference of >3.0 kcal/mol is also computed for carbamidyl radicals with other halogen atom substitution (X = Br, I). Compared to Cl-substitution, the vinylic OMe or SEt substitution lowers the activation energies for 6-*endo* cyclization (entries 15 and 16, Table 5). This could be attributed to the enhanced electron density of the C=C bond with OMe or SEt substitution. Note that the changes in activation energy coincide well with the outcome of cyclization observed experimentally (entries 6−8, Table 1). The above calculation data are in good agreement with the experimental results. The only exception is that, with OMe substitution, the calculated activation energy difference is only 1.4 kcal/mol while exclusive 6-*endo* cyclization was observed. A plausible explanation is that thermodynamic factors might also contribute to the control of regioselectivity in this case.[15] For radical **A** (R = OEt, X = H), the 5-*exo* and 6-*endo* cyclization are exothermic by 13.2 and 16.2 kcal/mol, respectively. As a comparison, the corresponding cyclizations of radical **A** (R = OEt, X = OMe) are less exothermic (7.2 and 12.3 kcal/mol, respectively) and the gap between 5-*exo* and 6-*endo* cyclization becomes larger, which increase the extent of thermodynamic control on the regioselectivity.

The calculations also help us to elucidate the unique role of heteroatom substitution. While the activation energies for 6-*endo* cyclization of carbamidyl radicals remain in the range of 7.0−7.7 kcal/mol, significant changes in the activation energy for 5-*exo* cyclization are computed from methyl to halogen substitution (entries 2 and 12−14, Table 5). This is unlikely to result from the steric factors (see also structure **20**). The difference between the methyl moiety and a heteroatom is that the latter bears lone pair electrons. Once a nitrogen-centered radical adds to a C=C bond having an internal heteroatom substituent, it will face the lone pair−lone pair electron repulsion between the nitrogen radical and the heteroatom. As can be seen from the transition state structures **19** and **20**, the N−Br distance in **20** (5-*exo*) is computed to be 3.069 Å, well within the range of close interaction. On the other hand, the N−Br distance in **19** (6-*endo*) is much longer (3.802 Å). Therefore, the lone pair electron repulsion is much stronger in 5-*exo* cyclization than in 6-*endo* cyclization. As a result, the activation energies for 5-*exo* cyclization are significantly increased by the presence of the heteroatom, leading to the overwhelming predominance of 6-*endo* cyclization. A similar discussion based on lone pair electron repulsion was found to successfully explain not only the regioselectivity of sulfonamidyl and aminyl radical cyclization, but also the chemoselectivity in the electrophilic halocyclization of unsaturated amides with vinylic halogen substitution,[16] implying the ubiquity of lone pair electron repulsion in the chemistry of vinyl halides toward heteroatom-centered reactive species.

Conclusion

The chemistry detailed above has provided a clear understanding on the behaviors of unsaturated amidyl radicals. The substituents attached to the carbonyl (R in **A**) significantly alter the reactivity of amidyl radicals toward intramolecular addition to the C=C bond. More electrophilic amidyl radicals are generally more prone to cyclization. Our experimental investigation in combination with theoretical analyses has pointed out that carbamidyl radicals are the superior choice for efficient cyclization. Moreover, the regioselectivity of cyclization can be well controlled by vinylic heteroatom substitution. As a result, highly regioselective 5-*exo*, 6-*endo*, 6-*exo*, and even 7-*endo* cyclization could be implemented. This finding should be an important application in the synthesis of cyclic amines.

Experimental Section

Typical Procedure for Bu_3SnH-Initiated Amidyl Radical Cyclization Reactions. Ethyl *N*-phenylthio-4-methylpent-4-enylcarbamate (**1d**, 279 mg, 1.0 mmol) was dissolved in 80 mL of anhydrous benzene, and the solution was brought to reflux. The mixture of Bu_3SnH (0.4 mL, 1.5 mmol) and AIBN (49 mg, 0.3 mmol) in benzene (20 mL) was added over a period of 4 h with the aid of a syringe pump under nitrogen atmosphere. The mixture was refluxed for an additional 1 h and then cooled to room temperature. After removal of the solvent under reduced pressure, the residue was chromatographed on silica gel with hexane−ethyl acetate (20:1, v:v) as the eluent to give piperidine **2d** (92 mg, 54% yield) and pyrrolidine **3d** (34 mg, 20% yield). **2d**: Colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87−0.89 (3H, m), 1.03−1.10 (1H, m), 1.23−1.28 (3H, m), 1.42−1.61 (3H, m), 1.77−1.80 (1H, m), 2.39 (1H, br), 2.67−2.76 (1H, m), 4.00−4.13 (4H, m). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.6, 18.7, 24.7, 30.8, 32.8, 44.1, 51.1, 60.9, 155.4. EIMS: *m*/*z* (rel intensity) 171 (M^+, 15), 156 (2), 142 (100), 126 (9), 116 (18), 98 (58), 69 (13), 56 (28). Anal. Calcd for $C_9H_{17}NO_2$: C, 63.13; H, 10.01; N, 8.18. Found: C, 63.01; H, 9.74; N, 8.19. **3d**: Colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22−1.30 (3H, m), 1.40/1.34 (6H, s), 1.72−1.80 (4H, m), 3.40−3.51 (2H, m), 4.04−4.19 (2H, m). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.4/14.3, 21.8/21.5, 25.7/26.7, 41.4/42.5, 47.3/48.2, 59.5/60.0, 60.2/59.7, 153.7/155.0. EIMS: *m*/*z* (rel intensity) 171 (M^+, 2), 156 (61), 128 (17), 112 (18), 84 (100), 70 (8), 55 (21), 47 (27). Anal. Calcd for $C_9H_{17}NO_2$: C, 63.13; H, 10.01; N, 8.18. Found: C, 62.82; H, 9.86; N, 8.24.

Typical Procedure for the Reactions of Amides with $Pb(OAc)_4/I_2$. To the solution of $Pb(OAc)_4$ (155 mg, 0.35 mmol) in dry dichloromethane (3 mL) was added iodine (64 mg, 0.25 mmol) at rt under nitrogen atmosphere. The mixture was stirred at rt for 5 min. *N*-(4-Bromopent-4-enyl)acetamide (**7c**, 21 mg, 0.1 mmol) was then added. The reaction mixture was irradiated at rt for 1 h with the aid of a 125 W high-pressure mercury lamp. The light was then turned off and aqueous $Na_2S_2O_3$ (10 mL) was added. The two layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layer was washed with aqueous Na_2CO_3 and brine and then dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel with hexane/ethyl acetate (20:1, v:v) as the eluent to give the product **8c** as a yellowish oil. Yield: 20 mg (60%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55−1.86 (2H, m), 2.18/2.14 (3H, s), 2.42−2.50 (1H, m), 2.64−2.73 (1H, m), 3.46−3.73 (2H, m), 3.86/4.04 (1H, 2d, J = 14.4 Hz), 4.06/4.25 (1H, 2d, J = 14.4 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 21.4, 25.3/26.1, 38.0/36.3, 40.9/45.8, 50.2/50.0, 65.4/60.2, 169.2/169.0. EIMS: *m*/*z* (rel intensity) 332 ($M^+ + 1$, 9), 252 (1), 206 (53), 204 (50), 164 (70), 162 (69), 83 (100), 43 (74). HRMS calcd for $C_7H_{11}OBrIN$ (M) 330.9069, found 330.9067.

Typical Procedure for the Reactions of Unsaturated Amides with DIB/I_2. To the solution of DIB (64 mg, 0.2 mmol) in dry CH_2Cl_2 (3 mL) was added iodine (38 mg, 0.15 mmol) at rt under nitrogen atmosphere. The mixture was stirred at rt for 5 min. Ethyl 4-iodopent-4-enylcarbamide (**7g**, 32 mg, 0.1 mmol) was added and the resulting mixture was irradiated at rt for 2 h with the aid of a 125 W high-pressure mercury lamp. Aqueous $Na_2S_2O_3$ (5 mL) was then added. The two layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layer was washed with aqueous Na_2CO_3 and brine, and then dried over anhydrous

Na_2SO_4. After removal of the solvent, the crude product was purified by column chromatography on silica gel with hexane/ethyl acetate (20:1, v:v) as the eluent to give the product **8g** as a yellowish oil. Yield: 27 mg (67%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (3H, t, J = 7.0 Hz), 1.57−1.62 (2H, m), 2.41 (2H, t, J = 5.6 Hz), 3.45 (2H, t, J = 5.1 Hz), 3.82 (2H, s), 4.12 (2H, q, J = 6.9 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 7.7/6.7, 14.7, 26.6, 43.0/43.3, 52.1, 61.8, 64.7/64.5, 154.7. ESI-MS: m/z (rel intensity) 410 (M^+ + 1), 432 (M^+ + Na). HRMS calcd for $C_8H_{14}NO_2I_2$ (M + H) 409.9108, found 409.9117.

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Supporting Information Available: Characterizations of compounds **1**−**18** and calculation results on **A**−**C**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) For a similar discussion, see: Alabugin, I. V.; Manoharan, M. *J. Am. Chem. Soc.* **2005**, *127*, 9534.

(16) Hu, T.; Liu, K.; Shen, M.; Yuan, X.; Tang, Y.; Li, C. *J. Org. Chem.* **2007**, *72*, 8555.