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Photochemical Rearrangement of *N*-Chlorolactams: A Route to *N*-Heterocycles through Concerted Ring Contraction

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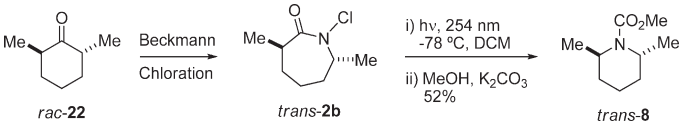

rac-**22** *trans*-**2b** *trans*-**8**

We report a novel ring contraction allowing the direct conversion of *N*-chlorolactams to their corresponding ring-contraction *N*-heterocycles upon photolysis. Results show that the rearrangement occurs with a variety of *N*-chlorolactams and that the greater the substitution at the migrating carbon, the greater the yield of product. Importantly, stereochemistry at the migrating carbon is conserved in the product. Rearranged products were isolated as their methyl carbamates in yields varying from 17% to 58%, with the major side product being the recyclable parent lactam.

Introduction

N-Heterocycles bearing a chiral tertiary or quaternary center next to nitrogen are found ubiquitously in nature and are often important pharmaceutical agents due to their large spectrum of biological activities.[1] Therefore, there has been much interest in the development of new methods for the synthesis of these types of cyclic subunits.[2] Those where the nitrogen atom is attached to a quaternary carbon are even more difficult to construct.[3]

The stereospecific rearrangement of chiral carboxylic acid derivatives has been used as a strategy to make chiral amine derivatives for many years (Scheme 1). A variety of rearrangements, such as the Curtius,[4] Hofmann,[5] Lössen,[6] and Schmidt[7] rearrangements,[8] offer a mild and predictable way to construct such carbon−nitrogen bonds. However, only acyclic amine derivatives can be prepared by these methods, one exception being the Hofmann rearrangement of cyclic imides.[9] The latter most likely involves an acyclic intermediate generated by the ring opening of the cyclic imide. Cyclization therefore follows the generation of the chiral C−N bond in those cases.

Accessing *N*-heterocycles directly from cyclic amides under mild conditions would thus be complementary and highly desirable. We now report that this is possible by the photochemical ring contraction of *N*-chlorolactams **I**.[10] Edwards and collaborators photolyzed and thermolyzed steroid derivatives *N*-mesyloxy-4-aza-cholestane-3-ones

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(4) (a) Banthorpe, D. V. *The Chemistry of the Azido Group*; Patai, S., Ed.; Wiley: New York, 1971, 640 pp. (b) Smith, P. A. S. *Org. React.* **1946**, *3*, 337–449. (c) Leogane, O.; Lebel, H. *Synthesis* **2009**, *11*, 1935–1940.

(5) For selected reviews, see: (a) Walis, E. S.; Lane, J. F. *Org. React.* **1946**, *3*, 267–306. (b) Senanayake, C. H.; Fredenburg, L. E. *J. Am. Chem. Soc.* **1994**, *116*, 7947–7948. (c) Gogoi, P.; Konwar, D. *Tetrahedron Lett.* **2007**, *48*, 531–533.

(6) Bauer, L.; Exner, O. *Angew. Chem., Int. Ed.* **1974**, *13*, 376–384.

(7) For selected books and reviews, see ref 4a and (a) Wolff, H. *Org. React.* **1946**, *3*, 307–336. (b) Lang, S.; Murphy, J. A. *Chem. Soc. Rev.* **2006**, *35*, 146–156.

(8) For a related rearrangement (Stieglitz), see: (a) Gassman, P. G.; Fox, B. L. *J. Am. Chem. Soc.* **1967**, *89*, 338–342. (b) Hoffmann, R. V.; Kumar, A.; Buntain, G. A. *J. Am. Chem. Soc.* **1985**, *107*, 4731–4736.

(9) See, for example: Jianga, X.; Wanga, J.; Hua, J.; Gea, Z.; Hua, Y.; Hua, H.; Covey, D. F. *Steroids* **2001**, *66*, 655–662.

(10) For a preliminary communication on this subject, see: Drouin, A.; Lessard, J. *Tetrahedron Lett.* **2006**, *47*, 4285–4288.

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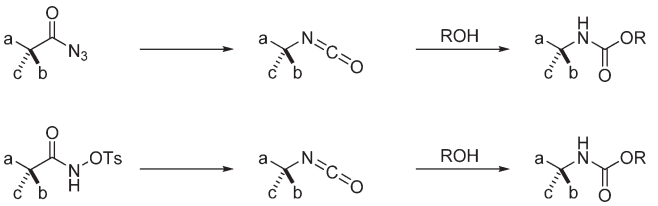
SCHEME 1. Stereospecific Rearrangements of Carboxylic Acid Derivatives



and observed the undesired (in their case) formation of ring-contraction carbamates (35%).[11] To the best of our knowledge there has been no further study of this rearrangement.

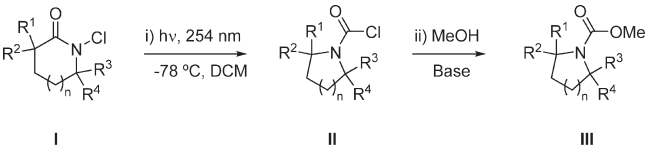
Unlike other conceptually similar rearrangements, this one is only applicable to cyclic systems. Reaction conditions are very mild (−78 °C) and *N*-chlorolactams can be prepared directly from the *N*-chlorination of lactams. The latter can be accessed in racemic or enantiomerically pure form using a variety of methods: cyclization of γ- and ε-amino acid derivatives,[12] cyclization of amidyl radicals,[13] Pd-catalyzed ring formation,[14] or even ring expansion from cyclic ketones via the Beckmann rearrangement.[15] The introduction of specific chiral centers α to the lactam carbonyl can be done through a plethora of methods.[16] Some methods allow for the preparation of lactams bearing a chiral center next to the nitrogen atom.[17] We report herein our investigation of the scope and limitations of this novel methodology.

Results and Discussion

All required *N*-chlorolactams **I** were synthesized in 1−8 steps from commercially available starting materials or from known amides (see Supporting Information). Irradiations were carried out in dichloromethane at −78 °C in a Rayonet apparatus at 254 or 300 nm, and the carbamoyl chloride intermediates **II** obtained were then treated with methanol and base (Et_3N or K_2CO_3) to yield the desired rearranged methyl carbamates **III** (Scheme 2). Some carbamoyl chloride intermediates **II** could be isolated, but many decomposed upon chromatography.

Investigation of the Effect of Lactam Structure on the Rearrangement. We first irradiated *N*-chlorolactams **1a**−**4a** to evaluate the effect of ring size on the ring contraction (Scheme 3). Six- and seven-membered *N*-chlorolactams **1a**

SCHEME 2. Photochemical Ring Contraction of *N*-Chlorolactams



SCHEME 3. *N*-Chlorolactams Used in the Investigation of the Effect of Ring Size on the Photochemical Rearrangement

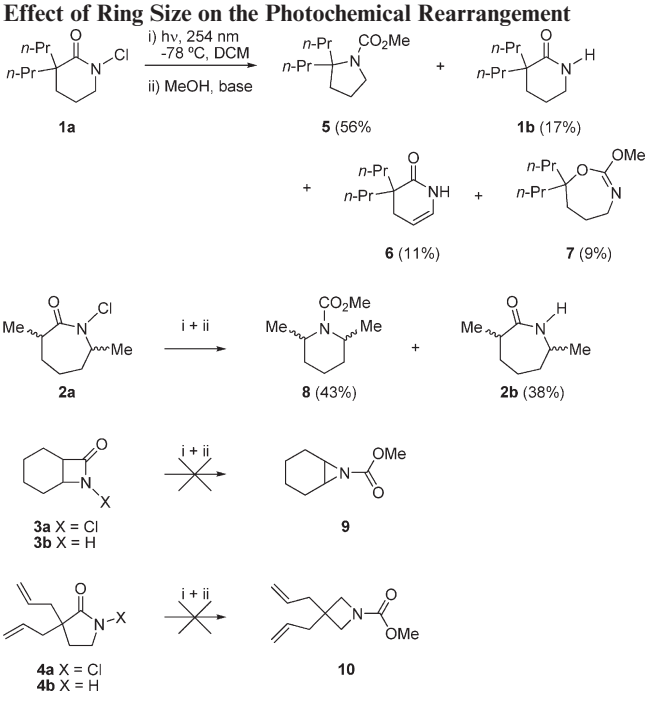


TABLE 1. Results Obtained from the Irradiation of *N*-Chlorolactams 1a−4a, 11a, and 12a of Varying Ring Sizes

entry	*N*-chlorolactam	product (yield)[a]	parent lactam (yield)[a]	other products (yield)[a]
1	**1a**	**5** (56%)	**1b** (17%)	**6** (11%) + **7** (9%)
2	**2a**	**8** (43%)	**2b** (38%)	
3	**3a**	**9** (0%)	**3b** (0%)	decomposition
4[b]	**4a**	**10** (0%)	**4b** (99%)	
5	**11a**	**13** (48%)	**11b** (32%)	
6	**12a**	**14** (57%)	**12b** (18%)	

[a]Isolated yields unless specified. [b]See ref [23a].

and **2a** underwent the rearrangement in moderate yields (Table 1, entries 1 and 2). The main accompanying side products were the parent lactams **1b** and **2b**, respectively. The issue of stereochemistry in the rearrangement of **2a** will be discussed later. β-*N*-Chlorolactam **3a** did not undergo the rearrangement under the conditions surveyed (Table 1, entry 3). It later became clear that the fused six-membered ring in **3a** did not impede the rearrangement and that the increase in ring strain is responsible for this failure. No ring contraction occurred when *N*-chloro-γ-lactam **4a** was irradiated (entry 4). The parent lactams **1b**−**4b** (17−99%) are likely formed by intermolecular hydrogen abstraction either from the solvent or from the substrate (see discussion in the mechanistic section of the paper). The parent lactams can, however, easily be recycled to the starting *N*-chlorolactams through simple chlorination (see Experimental Section) and therefore can be resubmitted to

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(13) For selected reviews, see: (a) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543–17594. (b) Yuan, X.; Liu, K.; Li., C. *J. Org. Chem.* **2008**, *73*, 6166–6171.
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(16) For selected books and reviews, see: (a) Spino, C. *Org. Prep. Proc. Int.* **2003**, *35*, 1–140. (b) Arya, P.; Qin, H. *Tetrahedron* **2000**, *56*, 917–947. (c) Juaristi, E. *Introduction to Stereochemistry and Conformational Analysis*; Wiley & Sons: New York, 1991; 331 pp. (d) Casimir, J. R.; Didierjean, C.; Aubry, A.; Rodriguez, M.; Briand, J.-P.; Guichard, G. *Org. Lett.* **2000**, *2*, 895–897. (e) Murray, P. J.; Starkey, I. D. *Tetrahedron Lett.* **1996**, *37*, 1875–1878. (f) Hanessian, S.; Reinhold, U.; Gentile, G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1881–1884. (g) Battistini, L.; Rassu, G.; Pinna, L.; Zanardi, F.; Casiraghi, G. *Tetrahedron: Asymmetry* **1999**, *10*, 765–773.
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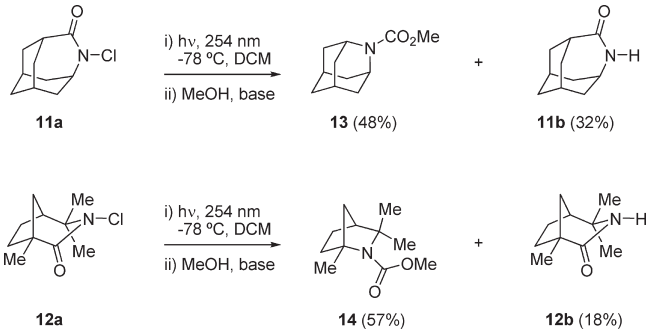
SCHEME 4. Irradiation of Bridged Polycyclic Molecules



SCHEME 5. *N*-Chlorolactams Used in an Investigation of the Effect of Substitution α to the Carbonyl on the Photochemical Rearrangement

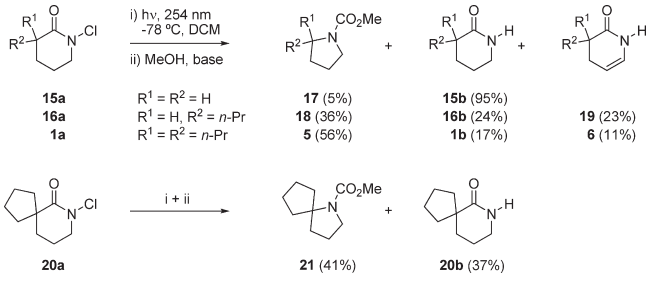


TABLE 2. Results Obtained from the Irradiation of *N*-Chlorolactams 1a, 15a, 16a, and 20a of Varying Substitution α to the Carbonyl

entry	*N*-chlorolactam	product (yield)[a]	parent lactam (yield)[a]	other products (yield)[a]
1	**15a**	**17** (5%)[b]	**15b** (95%)[b]	
2	**16a**	**18** (36%)	**16b** (24%)	**19** (23%)
3	**1a**	**5** (56%)	**1b** (17%)	**6** (11%) + **7** (9%)
4	**20a**	**21** (41%)	**20b** (37%)	

[a]Isolated yields unless specified. [b]Ratio determined by GC.

the photolytic conditions to yield more of the desired product. In the case of **1a**, an 11% yield of enamide **6**, originating from radical chlorination followed by HCl elimination, was isolated. Its formation, as well as the formation of byproduct **7**, will be discussed in the mechanistic section of the manuscript.

Bridged polycyclic molecules rearranged with similar efficiency (Scheme 4 and Table 1, entries 5 and 6). Possibly, a decrease in ring strain, in going from reactants to products, helped in these cases, but nevertheless it seems that the ring structure of the lactam can be quite varied without a detrimental effect on the yield of the reaction. We suspected that the nature of the migrating carbon might influence to a larger degree the efficiency of the rearrangement compared with other structural features and proceeded to investigate this aspect.

We thus irradiated precursors **1a** and **15a**−**16a** (Scheme 5) to evaluate the importance of the degree of substitution on the carbon α to the amide carbonyl on the yield of the ring-contraction product. The rearranged products **5**, **17**−**18**, isolated as the methyl carbamates, and the parent lactams **1b**, **15b**−**16b** accounted for 60−81% of the isolated products (Table 2). As we suspected, the degree of substitution at the migrating carbon greatly affects the yield of the rearrangement product. The examples in entries 1 to 3 of Table 2 clearly demonstrate the impact of carbon substitution on the ring contraction as the unsubstituted case gave a mere 5% of rearrangement product (entry 1), whereas the disubstituted case gave 56% of the corresponding ring-contraction product (entry 3). The spiro system **20a** also underwent the rearrangement with similar efficiency (entry 4). The monosubstituted *N*-chlorolactam **14a** gave an intermediate yield of 36% (entry 2). Therefore, carbons that have a higher degree of substitution possess a greater propensity to migrate. This parallels trends in rearrangements such as the Beckmann[18] and the Baeyer−Villiger reactions,[19] and to some extent we believe that the present rearrangement shares mechanistic similarities (*vide infra*).

The question of the stereochemistry at the migrating carbon is of high importance if this rearrangement is to be used in synthesis. To assist in this assessment, we prepared *N*-chlorolactam *cis*-**2a** and *trans*-**2a** in the racemic form and separated them (Scheme 6). The relative stereochemistry of the lactams *cis*-**2b** and *trans*-**2b** was unambiguously assigned from a single crystal X-ray diffraction analysis of *trans*-**2b** (see Supporting Information). Upon photolysis, *cis*-**2a** led to a 43% yield of *cis*-**8**, and *trans*-**2a** afforded 52% of *trans*-**8**.[20] The rearrangement is thus stereospecific, and this fact, although not so surprising, is extremely important from the point of view of the synthesis of natural products and from a mechanistic point of view as well (*vide infra*). The sequence of reactions shown in Scheme 6 also underscores the potential power of our methodology as we are able to transform the chiral cyclic ketones **22** into chiral *N*-heterocycles **8** in four steps (although, in this particular case, *cis*-**8** happens to be *meso*).

The next logical step, after examining the effect of the number of substituents α to the carbonyl, was to investigate the consequence of the nature of those substituents. To that effect, *N*-chlorolactams **24a**−**28a** were prepared and submitted to photolysis. Results are shown in Scheme 7 and Table 3. The substrates with electron-donating substituents (entries 1, 3, and 4) yielded rearranged product with little or no formation of the parent lactam, which initially was taken as an excellent improvement. However, a side product stemming from a fragmentation into an isocyanate (Scheme 8) was isolated in these three cases. We believe that the increased yields of acyclic acetal-carbamates **34**, **36**, and **37** are due to the π-donor nature of these substituents, which stabilizes a carbocation intermediate (see **39**, Scheme 8). We observed very little formation, if at all, of chlorinated byproduct, a result that has mechanistic significance (*vide infra*). Less electron-donating groups (AcO in **25a**, entry 2) did not produce acyclic carbamate **35** but did yield much parent lactam **25b**. The silyl group (entry 5) behaved much like any alkyl group.

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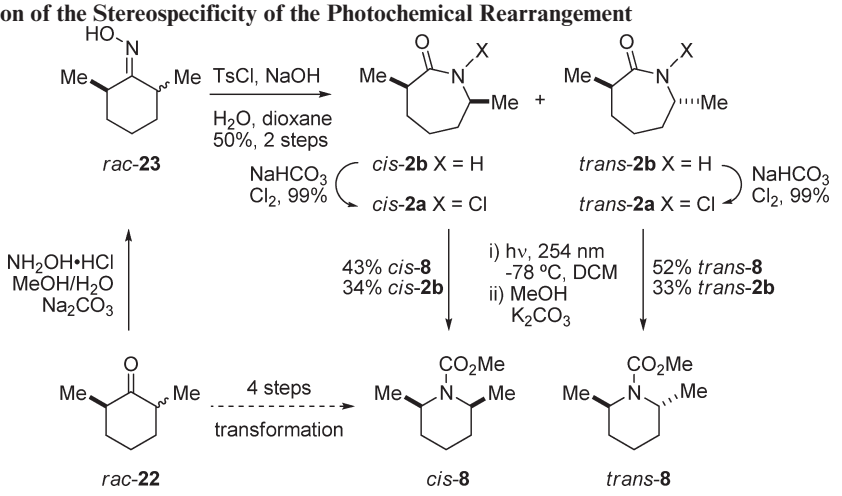
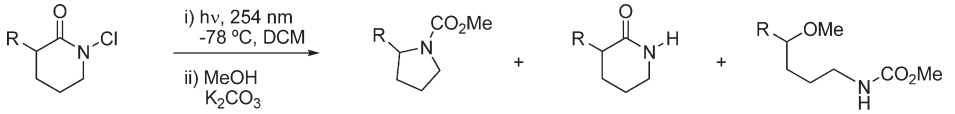
(19) Renz, M.; Meunier, B. *Eur. J. Org. Chem.* **1999**, 737–750.

(20) The stereochemistry of *cis*-**2b** was inferred from its conversion to *cis*-**8**, which was independently prepared from commercial *cis*-2,5-dimethylpiperidine (see Experimental Section). We verified the absence of the other stereoisomer in each experiment by analysis of the NMR spectra of the crude reaction mixtures.

SCHEME 6. Investigation of the Stereospecificity of the Photochemical Rearrangement



SCHEME 7. *N*-Chlorolactams Used in an Investigation of the Effect of Substitution α to the Carbonyl on the Photochemical Rearrangement



24a R = OMe
25a R = OAc
26a R = OPh
27a R = O(*p*-MeOPh)
28a R = $SiMe_3$

29 (26%)
30 R=OH+OMe (45%)
31 (42%)
32 (53%)
33 31%)

24b (8%)
25b (37%)
26b (0%)
27b (0%)
28b (25%)

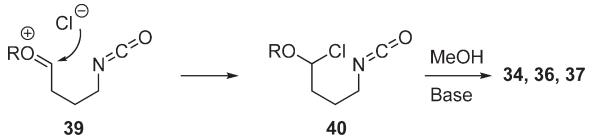
34 (51%)
35 (0%)
36 (37%)
37 (24%)
38 (0%)

TABLE 3. Results Obtained from the Irradiation of *N*-Chlorolactams 24a−28a

entry	*N*-chlorolactam	product (yield)[a]	parent lactam (yield)[a]	acyclic carbamate (yield)[a]
1	**24a**	**29** (26%)	**24b** (8%)	**34** (51%)
2	**25a**	**30** (45%)[b]	**25b** (37%)[c]	**35** (0%)
3	**26a**	**31** (42%)	**26b** (0%)	**36** (37%)
4	**27a**	**32** (53%)	**27b** (0%)	**37** (24%)
5	**28a**	**33** (31%)	**28b** (25%)[d]	**38** (0%)

[a]Isolated yields unless specified. [b]Isolated as a mixture of **30**, R = OH and R = OMe. [c]Isolated as **25b**, R = OH. [d]Determined by NMR on crude mixture because of instability of the product upon purification.

SCHEME 8. Proposed Mechanism for the Formation of the Acyclic Carbamates 34, 36, and 37

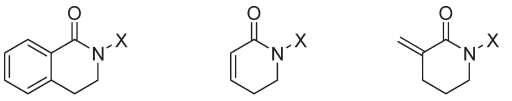


39 **40**

As in all rearrangements of this type, with the exception of aromatic rings, sp^2-hybridized carbons do not migrate.[4−7] We thus submitted *N*-chlorolactams **41a−43a** to the photolytic conditions (Scheme 9), and as expected, the parent lactams **41b−43b** were the only products isolated in each of these three cases.

Preliminary Foray into the Mechanistic Aspect of the Rearrangement. The trends we found, namely, that the rearrangement is concerted, that carbons capable of stabilizing a positive charge have a greater migrating ability, and that alkenes do not migrate, indicate that our photochemical rearrangement shares mechanistic similarities with other rearrangements of this type (Lössen, Schmidt, etc.).

SCHEME 9. Carbons That Are sp^2-Hybridized Do Not Migrate



41a X = Cl
41b X = H

42a X = Cl
42b X = H

43a X = Cl
43b X = H

However, in each of these rearrangements, the mechanism always involves a reactive intermediate of type **I**, **II**, or **III** (Figure 1), none of which can be part of a ring structure. There are examples of base-promoted Schmidt rearrangements of cyclic imides, but it is likely that an acyclic intermediate of type **II** is involved in those cases, from cleavage of one imide bond.[9] We tested, of course, the photochemical rearrangement of acyclic *N*-chloroamides, under identical reaction conditions, and to our initial surprise, no contraction product was observed but only the parent lactam. It thus appears that an acyclic intermediate, whether an excited state of the *N*-chlorolactam (**IV**), an amidyl radical **V**, or a *N*-acylnitrenium ion **VI**, does not allow a proper orbital alignment for the migration to occur. In a *N*-chlorolactam **VII**, this alignment is *de facto* maintained.

The mechanistic map for this reaction is vast, and Scheme 10 gives an overview of it. Let us state immediately that Favorskii-like mechanisms or intermediates are precluded on the basis of the result of Table 1 entries 1 and 6 as well as Table 2 entry 4. Such Favorskii-like intermediates are implied, for example, in the base-promoted rearrangement of *N*-(sulfonyloxy)amides to the corresponding α-amino amides, but the presence of a hydrogen β to the carbonyl is required.[21]

(21) Hoffman, R. V.; Nayyar, N. K.; Chen, W. *J. Org. Chem.* **1995**, *60*, 4121–4125. and references therein.

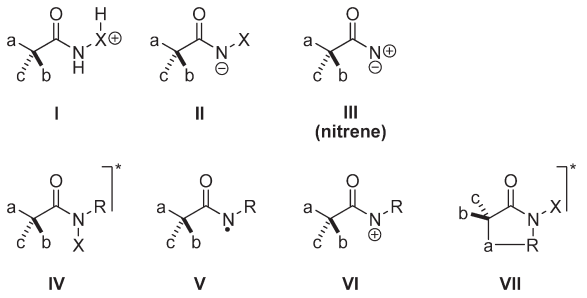


FIGURE 1. Postulated or known reactive intermediates.

The rearrangement occurs with equal efficiency at 254 or 300 nm wavelengths, all of which are weakly absorbed by the *N*-chlorolactam **44** to give an excited state **45**. Little is known about the photochemical transition of *N*-chlorolactams that leads to the homolytic cleavage of the N−Cl bond or perhaps, in our case, directly to the rearrangement. The UV spectrum of *N*-chloroamides and *N*-chlorolactams (see Supporting Information) only show an end-absorption in acetonitrile, decreasing in intensity from 200 nm ($\varepsilon \approx 12\,000$ L mol^{-1} cm^{-1} for *N*-chlorolactam **1a**) to 350 nm ($\varepsilon \approx 0$). At 254 and 300 nm, the absorbance is weak with $\varepsilon = 464$ or 140 L mol^{-1} cm^{-1}, respectively. This behavior is similar to that of amides for which the absorption in the 220−230 nm region has been attributed to a n $\rightarrow \pi^*$ transition.[22] For *N*-chlorolactams, the end-absorption could possibly be due to a n $\rightarrow \sigma^*_{N-Cl}$ transition or to both transitions if they are close in energy. Further studies are required to determine the exact nature of the electronic transition.

We know that the products of the rearrangement are photochemically stable because we have resubmitted products **5**, **29**, and **30** to irradiation under the same conditions only to recover 80−95% of the starting material intact.

On the basis of early works by Lessard,[23] Kuehne[24] and others,[25] it is highly probable that **45**, after internal conversion or intersystem crossing decays, at least in part, to the radical pair **46** in a solvent cage. Indeed, Scheme 11 shows examples from these research groups of proven radical chain reactions of *N*-chloroamides or *N*-chlorolactams. Therefore, escape of the chlorine radical from the solvent cage and hydrogen abstraction on the substrate would explain some of the side products observed such as **6** and **19**. It would also explain the formation of the parent lactams **1b**, **2b**, **4b**, **11b**, **12b**, **15b**, **16b**, **20b**, **24b**, **25b**, **28b**, and **41b**−**43b**. Indeed, hydrogen abstraction generates HCl, and the latter, via a Goldfinger type mechanism,[26] yields the parent lactam. A control experiment in which external HCl was added to *N*-chlorolactam **11a** confirmed its complete and fast transformation into the corresponding parent lactam. The parent lactam and the chlorinated products can also be formed by intermolecular hydrogen abstraction from the amidyl radical (Bloomfield-type mechanism).[27]

However, it is highly unlikely that the rearrangement itself is radical in nature.[28] Its concertedness precludes it, as do results from the following series of experiments. Entries 1−6 of Table 4 show that when *N*-chlorolactams **11a,c**−**e** were submitted to different reaction conditions known to generate the amidyl radical,[29] only the parent lactam **11b** or decomposition products were obtained. Also, when **11a** was thermolyzed to generate the radical pair **46**, only the parent lactam **11b** or decomposition was observed (entries 7−9). In those cases, the parent lactam **11a** was likely formed by H-abstraction from either the solvent (entries 1−3, 7, and 9) or from tributyltin hydride (entries 4−6) by the amidyl radical depending on the reaction conditions.

Importantly, the presence of a double bond does not bring about cyclization of a purported radical intermediate **47** (Scheme 12). Such intermediates, generated by other methods, have been shown to cyclize onto double bonds in good yield, including a terminal double bond.[30] The fact that two prenyl units (**58a**) led to the formation of 8% of the polycyclic compounds **65a,b** but that no trace of the corresponding compound was obtained starting from the diallyl substrate **57a** indicates that a cationic intermediate **48** is more likely than a radical intermediate **47**. Indeed, cyclization to a tertiary carbocation would be more favorable than cyclization to a primary carbocation, but the difference between a tertiary and a primary radical is not so pronounced.[31]

Ionic species could be generated either from the decay of the electronic or vibrational excited state **45**, via a yet unknown mechanism, directly to the rearranged *N*-acylium ion **48** (Scheme 10) or via a single electron transfer from the lactamyl radical **46** to the chlorine atom inside the solvent cage with concomitant rearrangement to the *N*-acylium ion **48**. Whatever the case may be, we believe the transition state to be highly asynchronous as suggested by the effect of the substitution on the migrating carbon. A single electron transfer implying an lactamyl radical has been previously proposed by Edwards and collaborators,[11] and single electron transfer mechanisms between radical species have also been previously reported.[32] The *N*-acylium ion **48** is then trapped by the chloride ion in the solvent cage, and the resulting carbamoyl chloride **49** is converted to the corresponding methyl carbamate by basic methanol treatment.

It should be noted that the [1,2]-migration of the ring carbon can be assisted by the lone pairs of the carbonyl group, which are in the same plane as the migrating bond

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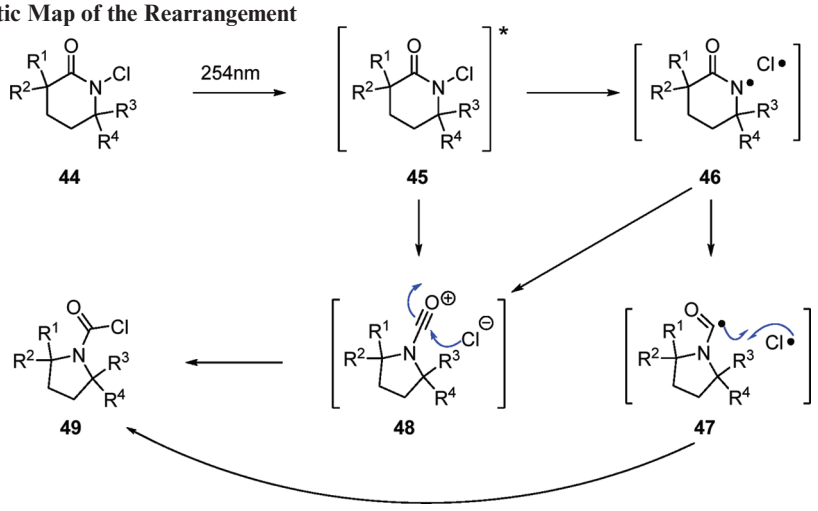
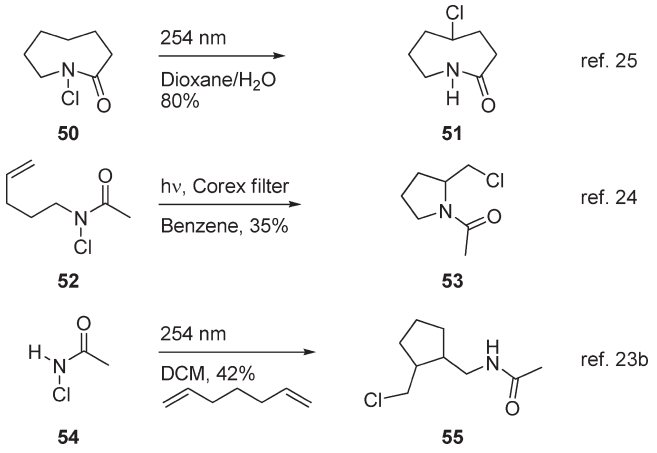
SCHEME 10. Mechanistic Map of the Rearrangement



SCHEME 11. Demonstrated Radical Chain Reactions of *N*-Chloroamides and *N*-Chlorolactams



(Figure 2, **45-A** or **46-A**).[33] Alternatively, with the presence of a strong π-donor or in cases where a stable tertiary carbocation could be formed, fragmentation to acetals (**34**, **36**−**37**) or oxazepines (**7** and **63**−**64**) may occur, similarly to the abnormal Beckmann rearrangement[34] (Figure 2, **45-B** or **46-B**). We verified that oxazepines **7** and **63**−**64** as well as acetals **34**, **36**−**37** were not produced "post-rearrangement" by resubmitting the carbamoyl chloride, isolated from the irradiation of *N*-chlorolactam **24a**, to photolysis and basic methanol treatment. Only the methyl carbamate **29** was obtained. Conversely, oxazepines **7** and **63**−**64** as well as acetals **34**, **36**−**37** did not recyclize to the corresponding methyl carbamates **5**, **29**, **31**, **32**, and **60**−**61**, respectively, under a variety of methanolic Lewis or Brønsted acid conditions.

A single electron transfer without concomitant rearrangement would generate an acylnitrenium ion **VI** (Figure 1), but this is an unlikely intermediate because such species are highly energetic and unstable according to experimental and computational studies.[35] In addition, the use of halophilic Lewis acids (Ag^{1+}, Al^{3+}) under various temperatures and solvents on substrate **11a** led to recovery of starting material in each case except one ($AlCl_3$ in benzene), where the parent lactam **11b** was produced quantitatively. We believe the latter conditions actually led to the electrophilic (ionic) chlorination of benzene. Silver(I) is known to assist the departure of halogen atoms in various reactions,[36] including *N*-chlorolactams.[37]

The capacity to rearrange to an acylnitrenium ion, where such species is stabilized, was tested with substrates **67a**, **68a**, and **69b** (Scheme 13). The isolation of products **72**−**74** substantiates the formation of an acylnitrenium.[38] These products were formed by an attack of the chloride ion *ortho* to nitrogen on intermediate **75**. In fact, lactam **69b** transformed instantly to **74** upon *N*-chlorination, but no ring-contraction product was isolated in this case. This strongly suggests that the formation of an acylnitrenium is not enough to produce a rearrangement, and it lends credence to the hypothesis that irradiation of *N*-chlorolactams **67a** and **68a** generates the corresponding excited state that either decays with concomitant rearrangement to **70** or **71**, respectively, or decays to the corresponding radical pair, which rearranges with concomitant electron transfer (see **46** → **48** in Scheme 10). Any stabilization of the amidyl radical might slow the rearrangement reaction by lowering the rate of electron transfer, which may explain the low yield of product

(33) In accord with published literature, we use the Σ_N electronic configuration of the amidyl radical. The latter is known to be involved in radical cyclizations. See: (a) Mackiewicz, P.; Furtoss, R.; Waegell, B.; Côté, R.; Lessard, J. *J. Org. Chem.* **1978**, *43*, 3746–3750. (b) Lessard, J.; Côté, R.; Mackiewicz, P.; Furtoss, R.; Waegell, B. *J. Org. Chem.* **1978**, *43*, 3750–3756. See also: (c) Lessard, J.; Griller, D.; Ingold, K. U. *J. Am. Chem. Soc.* **1980**, *102*, 3262–3264. (d) Sutcliffe, R.; Griller, D.; Lessard, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1981**, *103*, 624–628. (e) Sutcliffe, R.; Ingold, K. U.; Lessard, J. *J. Am. Chem. Soc.* **1981**, *103*, 7685–7686. (f) Danen, W. C.; Gellert, R. W. *J. Am. Chem. Soc.* **1972**, *94*, 6853–6854. (g) Koenig, T.; Hoobler, J. A.; Klopfenstein, C. E.; Hedden, G.; Sunderman, F.; Russel, B. R. *J. Am. Chem. Soc.* **1974**, *96*, 4573–4577.

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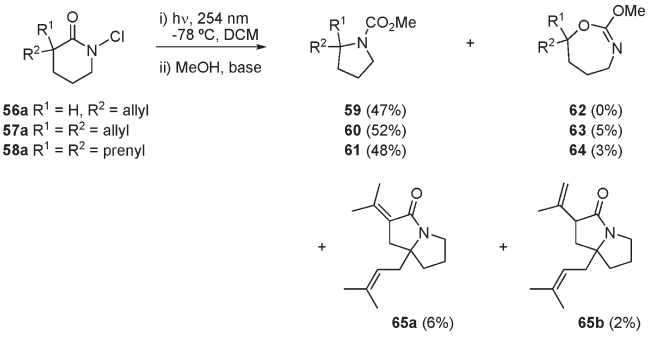
TABLE 4. Results Obtained from the Irradiation of *N*-Chlorolactams 11a,c−e

entry	lactam derivative	X	reaction conditions	product[a]
1	**11a**	Cl	$(Bu_3Sn)_2$, A*i*BN, DCM, −78 °C, 350 nm	**11b** and decomposition
2	**11a**	Cl	Bu_3SnH, A*i*BN, DCM, −78 °C, 350 nm	**11b** and decomposition
3	**11a**	Cl	Et_3B, O_2, DCM, −78 °C	**11b** as major product and decomposition
4	**11c**	SPh	A*i*BN, Bu_3SnH, PhH, reflux	**11b** only
5	**11d**	SC(S)OEt	Et_3B, O_2, DCM, −78 °C	**11b** as major product and decomposition
6	**11e**	N=O	DCM, −78 °C, 254 nm	**11b** only
7	**11a**	Cl	MeOH, 200 °C, 1 h	**11b** only
8	**11a**	Cl	neat, 200 °C, 1 h	**11b** only
9	**11a**	Cl	$PhCH_3$, 200 °C, 1 h	**11b** only

[a]Determined by NMR.

SCHEME 12. Interception of Cationic Intermediate 48 by an Internal Double Bond



70 and the even lower yield of product **71**. It is admittedly more difficult to explain the effect of the R group if the mechanism involves the decay of an excited state directly to the rearranged product (see **45** → **48** in Scheme 10).

Solvent should have a major effect on the efficiency of the rearrangement if polar intermediates are involved. We therefore undertook an exhaustive solvent screen and varied the temperature and wavelength. The list of solvents screened is shown in Table 5. Chlorinated solvents (entries 1−4) were generally better than the others, with dichloromethane being the best choice (entry 1). A fluorinated solvent could not dissolve the substrate (entry 5) like some nonpolar solvents (entry 6), and in such cases, irradiation left the reactant unchanged. Other nonpolar solvents lead to the exclusive formation of the parent lactam **11b** (entries 7−9). More polar solvents such as tertiarybutylmethyl ether, ethyl acetate, and acetonitrile gave significant amounts of rearranged product **13** (entries 11, 14, and 15), which seemed to indicate that polar intermediates are involved. However, highly polar solvents such as DMSO (entry 16), alcohols (entries 17−20), and water (entry 21) did not lead to any rearranged product, and acetic acid (entry 22) gave only traces of **13**. Irradiation of the neat substrate led to the formation of many chlorinated products (entry 23), as did some chlorinated solvents (entries 2−4) and DMSO (entry 16). It is therefore unclear at this stage if polar intermediates are involved.

If methanol (entry 17) and some alcoholic solvents (entries 18 and 20) are good hydrogen donors and could react with the chlorine radical in species like **46** to give HCl and hence the parent lactam, *tert*-butanol (entry 19) and water (entry 21) are not, and yet similar results were observed in those cases. In addition, viscous solvents (entries 19 and 20) and nonviscous solvents (entries 17 and 18) gave the same disappointing result, refuting the idea that viscous solvents could delay the chlorine radical's escape from the solvent cage and thereby favor the rearrangement.

Outlook. Currently, high yields of ring-contraction products can only be achieved through recycling of the parent lactam, obtained as a significant byproduct. However, we are very excited about the prospect of achieving higher yields for this reaction by replacing the chlorine with a mesyloxy or equivalent sulfonyloxy group. When compound **11f** was irradiated at 254 nm in methanol, a 72% yield of carbamate **13** was isolated *and no parent lactam was observed* (Scheme 14). The same reaction gave 58% of **13** in dichloromethane, still with no formation of the parent lactam. The reasons for this success are not yet clear, and we are currently exploring the generality of this important improvement as well as developing oxidation methods to convert lactams into hydroxamic acids.

The rearrangement of *N*-chlorolactams nicely complements existing methods to make C−N bonds from carboxylic acid derivatives. The possibility of replacing the carbonyl function of a chiral cyclic ketone by nitrogen while retaining the stereochemical information of the starting ketone is particularly attractive. Further developments are currently underway.

Experimental Section

(3*R,7*R**)-3,7-Dimethylazepan-2-one (*trans*-2a) and (3*R**,7*S**)-3,7-Dimethylazepan-2-one (*cis*-2b).** Commercial 2,6-dimethylcyclohexanone (*rac*-**22**) (2.00 g, 15.8 mmol) was dissolved in 60 mL of a 1:1 solution of methanol and water. The mixture was cooled to 0 °C, and $NH_2OH \cdot HCl$ (1.43 g, 20.6 mmol) was added, followed by Na_2CO_3 (3.36 g, 31.7 mmol). After 48 h of stirring at 0 °C, the mixture was heated to reflux temperature for 7 days. It was then cooled to room temperature and diluted with water, and the aqueous phase was extracted three times with Et_2O. The organic fractions were combined, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude oxime *rac*-**23** (2.22 g, 15.7 mmol, 98%), as a mixture of *cis* and *trans*, was used without further purification in the next step. It was dissolved in 50 mL of a solution of acetone and water (1:1). Then, aqueous NaOH (1.25 g, 31.3 mmol) was added, followed by *p*-toluenesulfonyl chloride (4.50 g, 23.5 mmol). The reaction mixture was stirred for 48 h. Then, acetone was evaporated under reduced pressure, and the aqueous was extracted with dichloromethane. The organic phases were combined, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give an oil. The oil was purified by flash chromatography on silica gel eluting with 50% ethyl acetate in hexanes gave lactams *cis*-**2b** (427 mg 20%) and *trans*-**2b** (683 mg, 7.86 mmol, 30%) as white solids. A portion of *trans*-**2b** was recrystallized from hexanes to obtain X-ray quality crystals. *trans*-**2b**: mp 76−77 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.49 (1H, br), 3.62−3.50 (1H, m), 2.80−2.68 (1H, m), 1.82−1.41 (6H, m), 1.24 (3H,

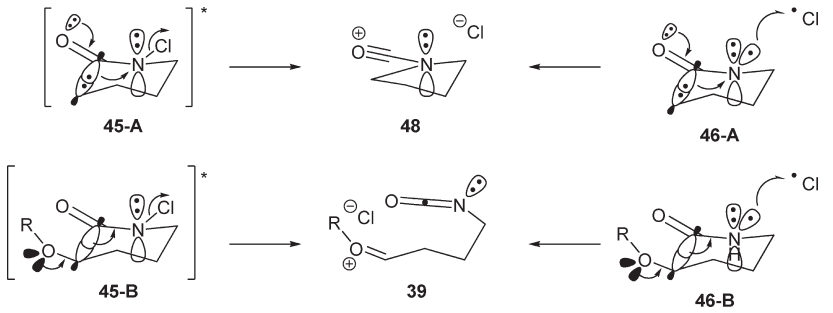


FIGURE 2. Electron transfer with concomitant migration of the carbon leading to rearranged products or fragmentation leading to side products.

SCHEME 13. Photolysis of *N*-chlorolactams 67a−68a and *N*-Chlorination of 69b

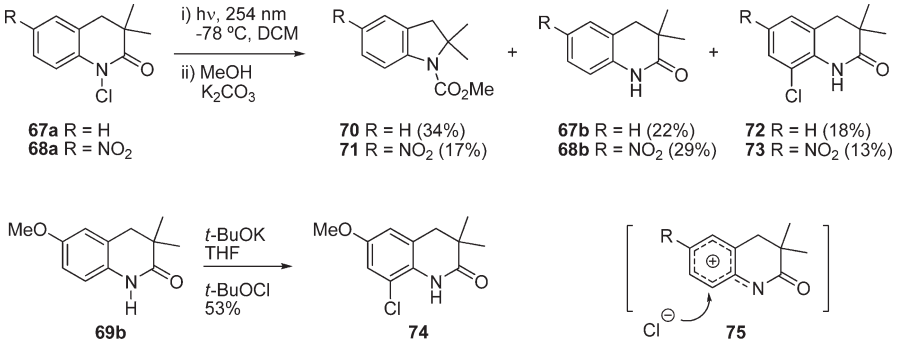


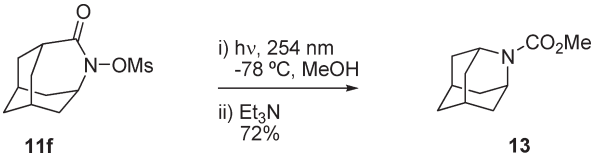
TABLE 5. Results Obtained from the Irradiation of *N*-Chlorolactam 11a in Various Solvents and at Different Wavelengths

entry	solvent[a]	wavelength	temp (°C)	ratio **11b**:**13**
1	DCM	254 nm	−78	3:5
2	DCE	254 nm	−15	4:3[b]
3	Cl_2C=CHCl	300 nm	−78	1:1[b]
4	CCl_4	300 nm	−15	> 20:1[b]
5	C_6F_{14}	insoluble		
6	pentane	insoluble		
7	cyclopentane	254 nm	−60	> 20:1
8	cyclohexane	254 nm	rt	> 20:1
9	benzene	300 nm	0	> 20:1
10	Et_2O	254 nm	−78	> 20:1
11	*t*-BuOMe	254 nm	−78	9:1
12	THF	254 nm	−78	> 20:1
13	dioxane	300 nm	rt	> 20:1
14	EtOAc	300 nm	−78	2:1
15	MeCN	254 nm	−40	1:1
16	DMSO	300 nm	rt	7:1[b]
17	MeOH	254 nm	−78	> 20:1
18	propanol	254 nm	−115	> 20:1
19	*t*-BuOH	300 nm	rt	> 20:1
20	$HO(CH_2)_2OH$	insoluble		
21	H_2O	254 nm	rt	> 20:1
22	AcOH	254 nm	rt	10:1
23	no solvent	254 nm	rt	> 20:1[b]

[a]Three different workups were carried out following photolysis: MeOH + Et_3N for entries 1, 4, and 21; MeOH, Na_2CO_3 for entries 2, 3, 8, 10, 11, 12, 14, and 16; no methanolic base treatment was performed for entries 7, 10, 13, 15, 17−19, and 21−23, and in those cases, **13** has CO_2Me=COCl. [b]The crude ^{1}H NMR displayed a variety of chlorinated products which were not fully characterized.

d, J = 7.4 Hz), 1.20 (3H, d, J = 6.7 Hz). *cis*-**2b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.37 (1H, br), 3.59−3.46 (1H, m), 2.63−2.47 (1H, m), 1.97−1.89 (1H, m), 1.77−1.57 (3H, m), 1.51−1.23 (2H, m), 1.19 (3H, d, J = 6.7 Hz), 1.13 (3H, d, J = 6.8 Hz).

SCHEME 14. Photolysis of *N*-Mesyloxylactam 11f



(3*R,7*S**)-1-Chloro-3,7-dimethylazepan-2-one (*cis*-2a).** To a stirring solution of *cis*-3,7-dimethyl-ε-caprolactam (*cis*-**2b**), (146 mg, 1.03 mmol) and $NaHCO_3$ (130 mg, 1.55 mmol) in H_2O (15 mL) was bubbled Cl_2 (g) until no more starting material was seen by TLC (1 h). The reaction mixture was then extracted with dichloromethane (3 × 20 mL). The organic layers were then combined and filtered through a small silica plug. The silica plug was washed with a small amount of EtOAc, and the filtrate was concentrated under reduced pressure to yield *cis*-**2a** as a clear oil (180 mg, 99%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 4.29−4.19 (1H, m), 2.93 (1H, ddq, J = 10.3, 6.7, 3.5 Hz), 1.77−1.49 (5H, m), 1.48−1.34 (1H, m), 1.42 (3H, d, J = 6.6 Hz), 1.20 (3H, d, J = 6.7 Hz).

(3*R,7*R**)-1-Chloro-3,7-dimethylazepan-2-one (*trans*-2a).** The same procedure as for *N*-chlorolactam *cis*-**2a** using *trans*-**2b** (197 mg, 1.39 mmol) and $NaHCO_3$ (176 mg, 2.09 mmol) gave *N*-chlorolactam *trans*-**2a** (244 mg, 1.39 mmol, 99%), as a clear oil. ^{1}H NMR (300 MHz, CDCl3) δ (ppm) 4.04 (1H, ddq, J = 13.4, 6.7 Hz), 2.59 (1H, ddq, J = 10.7, 7.0, 4.0 Hz), 2.05−1.95 (1H, m), 1.85−1.58 (4H, m), 1.51−1.40 (1H, m), 1.43 (3H, d, J = 7.0 Hz), 1.22 (3H, d, J = 6.7 Hz).

(2*R,6*S**)-Methyl 2,6-dimethylpiperidine-1-carboxylate (*trans*-8).** *N*-Chlorolactam *trans*-**2a** (240 mg, 1.37 mmol) was dissolved in dichloromethane (50 mL) and added into a quartz reaction cell. The reaction chamber was then placed into a Rayonet reactor chamber equipped with 254 nm UV lamps and exposed to UV light at −78 °C under N_2 atmosphere until no more starting

material was seen by TLC (6 h). The solution was then transferred to a stirred solution of MeOH (10 mL) and Et_3N (1 mL) at room temperature. The reaction mixture was allowed to stir for 18 h. The reaction was concentrated under reduced pressure to give an orange white solid. It was then taken up in diethyl ether, filtered, and concentrated under reduced pressure to yield a yellow oil. The crude product was purified by flash chromatography (5% EtOAC/95% hexanes to 100% EtOAc) to afford carbamate *trans*-**8** (121 mg, 52%) and parent lactam *trans*-**2b** (64 mg, 33%). *trans*-**8**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 4.03−3.96 (m,2H), 3.67 (s, 3H), 1.97−1.86 (m, 2H), 1.76−1.49 (m, 4H), 1.22 (d, 6H, J = 6.7 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 156.3 (s), 52.0 (d × 2 CH), 47.1(q), 26.3 (t × 2 CH_2), 20.7(t), 13.2(q, × 2 Me). IR ($CHCl_3$) ν (cm^{-1}) 2975, 1675. LRMS (m/z, relative intensity) 171, 156, 140, 102. HRMS calcd for $C_9H_{17}NO_2$ 171.1259, found 171.1253.

(2*R,6*R**)-Methyl 2,6-dimethylpiperidine-1-carboxylate (*cis*-8).** *N*-Chlorolactam *cis*-**2a** (176 mg, 1.00 mmol) was photolyzed as described above for the photolysis of *trans*-**2a**. The crude product was purified by flash chromatography (5% EtOAC/95% hexanes to 100% EtOAc) to afford carbamate *cis*-**8** (74 mg, 0.43 mmol, 43%) and parent lactam *cis*-**2b** (54 mg, 38%). *cis*-**8**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 4.38−4.25 (m, 2H), 3.69 (s, 3H), 1.83−1.37 (m, 6H), 1.19 (d, 6H, J = 7.0 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 156.3(s), 52.3(d × 2 CH), 45.9 (q), 30.0 (t × 2 CH_2), 20.8 (t), 13.7(q, × 2 Me). IR ($CHCl_3$) ν (cm^{-1}) 2996, 2948, 2868, 1673. LRMS (m/z, relative intensity) 171, 156, 140, 84. HRMS calcd for $C_9H_{17}NO_2$ 171.1259, found 171.1262.

cis-**8** was also prepared independently from commercial *cis*-2,5-dimethylpiperidine. Methyl chloroformate (151 μL, 1.95 mmol) was added dropwise to a stirring solution of commercially available *cis*-2,6-dimethylpiperidine (200 mg, 1.77 mmol) and triethylamine (370 μL, 2.66 mmol) in dichloromethane (10 mL) at 0 °C. A white precipitate formed, and the solution was allowed to warm to room temperature and monitored by TLC. The solution was then diluted with dichloromethane (50 mL) and washed sequentially with an aqueous solution of HCl (2 N) and a saturated solution of $NaHCO_3$. The organic layers was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield *cis*-**8** as clear oil (302 mg, quant). The characterization data of this compound was identical to the one obtained from the ring-contraction reaction described above.

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Supporting Information Available: Procedures and full spectral characterization for all new compounds and X-ray tables for compound *trans*-**2b**. This material is available free of charge via the Internet at http://pubs.acs.org.