Effects of Temperature on Atom Transfer Cyclization Reactions of Allylic α-Iodo Esters and Amides

Dennis P. Curran*,[1] and John Tamine

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

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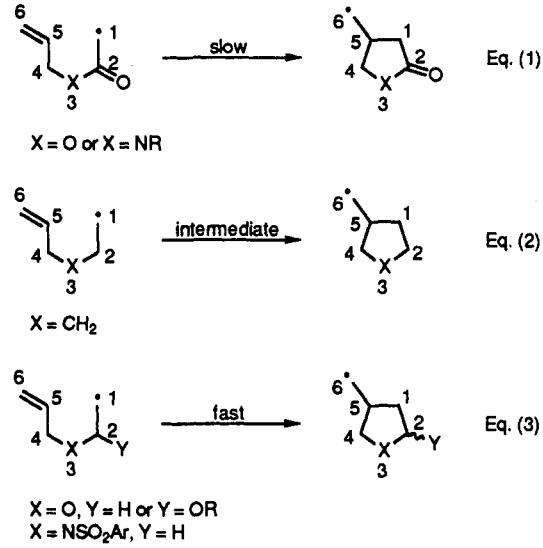
Atom-transfer cyclizations of allyl iodoacetates and *N*-allyl-*N*-methyliodoacetamides are much more efficient at 80 °C than at 25 °C. At 80 °C, β-(iodomethyl) lactones and lactams are formed rapidly and in good yield under standard atom-transfer conditions (sunlamp irradiation of iodide and 10% hexabutylditin in benzene for 10–60 min). It is proposed that this temperature effect is responsible for some unusual observations by Jolly and Livinghouse in the cyclization of *N*-cyclohexenyl-*N*-methyliodoacetamide. The results suggest that the beneficial effect of temperature arises because an increase in the rate of rotation of the OC–O or OC–N bond in the intermediate radicals begins to convert syn radicals (which cannot cyclize) to anti radicals (which can cyclize). Consistent with this hypothesis, the radical derived from *N*,*N*-diallyliodoacetamide (which always has a favorable arrangement for cyclization) closes with excellent efficiency at 25 °C.

Introduction

The cyclization of 3-heteroatom-substituted hexenyl radicals to form heterocycles is one of the most commonly used radical reactions in synthesis. Early on, it was discovered that substrates possessing both a heteroatom at C3 and a carbonyl group at C2 (eq 1) cyclized more slowly than their all-carbon parents (eq 2).[2] However, a lone C3 heteroatom generally accelerates radical cyclizations (eq 3),[3] and following the development of bromo acetal cyclizations by Stork[4] and Ueno,[5] synthetic applications of related cyclizations have flourished.[6] Lactams and lactones are usually produced from this strategy by oxidation of the products of radical cyclization. More recently, interest in the carbonyl-substituted analogues (eq 1) has been rekindled, and variation of substituents and reaction conditions has yielded several direct approaches to lactams[7] and lactones.[8] Despite this preparative progress, effects of substituents and reaction conditions in the cyclizations outlined in eq 1 are less well understood than those effects in the cyclizations in eqs 2 and 3.



We were lured into this area by an intriguing communication from Jolly and Livinghouse.[9] Figure 1 summarizes the results of their attempts to cyclize allylic α-iodo amide **1**. Standard tin hydride reduction at 0.02 M gave the desired lactam **2a** in 27% yield, alongside the reduced uncyclized amide **3** (54%). Irradiation under our standard ditin conditions[10] (0.1 equiv of hexabutylditin, sunlamp) gave only small amounts of **2b** and **3**, alongside recovered starting material (90%). However, increasing the amount of ditin to 0.7 equiv increased both the percent conversion

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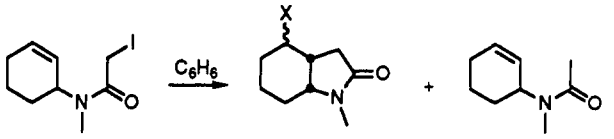
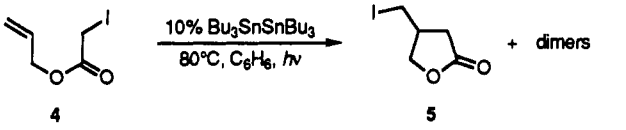


1	2a X = H 2b X = I	3
0.02 M, 1.1 eq Bu_3SnH	27% (2a)	54%
0.1 M, 0.1 eq $Bu_3SnSnBu_3$, *hν*	<3% (2b)	<6%
0.1 M, 0.7 eq $Bu_3SnSnBu_3$, *hν*	18% (2b)	40%
0.1 M, 0.55 eq $Bu_3SnSnBu_3$, 3.5 eq C_2H_5I, *hν*	68% (2b)	20%

Figure 1.

and the ratio of cyclic **2b** to acyclic **3** products. Further improvements resulted when alkyl iodides were added to the mixture, and optimum conditions involved sunlamp irradiation of **1** with 0.55 equiv of ditin and 3.5 equiv of ethyl iodide. The cyclic product **2b** formed in 68% isolated yield (exo/endo ratio 5.5/1), and the reduced product **3** formed in 20% yield. Jolly and Livinghouse suggested that the ethyl iodide might serve as a source of iodine atoms either toward the cyclic radical (to form the iodide **2b**) or toward the starting α-amidoyl radical. This latter reaction only re-forms the starting iodide, but because radicals with a (*Z*)-amide geometry may not be able to cyclize, this recycling of unproductive radical isomers to starting iodides might increase the yield.

We were puzzled by some of the observations and the rationalizations of Livinghouse and Jolly. We understood the different behavior of the tin hydride reduction of **1** and the atom-transfer cyclization of **1** under the standard conditions.[10] The radical cyclization step is not an integral part of the tin hydride chain; intermediate radicals are eventually reduced by tin hydride whether they cyclize or not. Thus, although it may be difficult to get a favorable ratio of cyclic/reduced products in a tin hydride reduction, it is not difficult to consume the starting iodide. In contrast, cyclization is an integral step in the atom-transfer chain: if it fails, then the chain breaks. The observations of Jolly and Livinghouse on the cyclization of **1** (poor conversion of starting iodide, consumption of ditin additive, products resulting from hydrogen abstraction) are typical for atom-transfer reactions that have a slow step in the chain.[11] The beneficial effect of excess ditin is not consistent with our proposal for the role of ditin in such reactions. We believe that the ditin serves either as an initiator or as a trap for iodine (a chain suppressent).[10a] The ultimate product from either of these reactions is inert tributyltin iodide. After the ditin is consumed, the iodine concentration builds up, and the chains shut down. It is important that the chain-propagation steps be considerably faster than initiation; otherwise one simply "irradiates away" the starting iodide to radical decomposition products and tributyltin iodide. Adding large amounts of ditin to a poorly propagating chain should increase the conversion, but it should not increase the efficiency of any of the chain steps. Furthermore, the yield bonus associated with addition of ethyl iodide was not easily understood. We doubted that either of the explanations that Jolly and Livinghouse put forth could be correct because the starting iodide **1** must be a significantly better iodine donor than ethyl iodide to either the initial radical or the cyclized radical.[12] Thus, in a normally propagating chain, ethyl



4	5	
0.3 M (one trial)†	8%	23%
0.03 M (average, four trials)†	35%	10%
0.003 M (average, two trials)†	40%	not observed
0.03 M (one trial)‡	41%	not isolated

† estimated by GC, using an internal standard
‡ isolated yield

Figure 2.

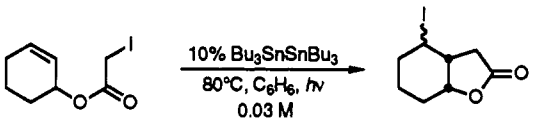


Figure 3.

iodide should be a spectator until its concentration greatly exceeds that of **1** (at which point the reaction is essentially over).

We suspected that the modified conditions of Jolly and Livinghouse had somehow increased the efficiency of the radical chains, and we felt that if we could identify the factor that caused this increase, we could extend the preparative usefulness of atom-transfer reactions. We now believe that the factor causing increased chain efficiency is temperature.

Results

Allyl iodoacetate (**4**) behaves like a typical recalcitrant substrate (Figure 2). Reduction of **4** with tributyltin hydride at 0.02 M gave only allyl acetate. Atom-transfer cyclization of **4** by the standard procedure[10] (0.3–0.03 M, 10% hexabutylditin, sunlamp irradiation) was not successful either. The ditin was quickly consumed (as indicated by the appearance of the characteristic color of molecular iodine), and at least eight new products of high molecular weight were formed (GC analysis). More than half of the iodide **4** remained at the end of such reactions. However, on varying the distance of the sunlamp from the reaction vessel, we noticed the formation of small amounts of **5** in some reactions where the vessel and the lamp were close (<10 cm). We quickly found that the increase in the yield of **5** resulted not from the increased light intensity, but from the warming of the reaction mixture by the lamp.

When the reaction mixture, with 10% hexabutylditin, was preheated to 80 °C and then irradiated, the GC yields of **5** and dimers resulting from bimolecular reactions[13] varied as a function of concentration, as indicated in Figure 2. At low concentrations (≤0.03 M), the slow radical cyclization competes effectively with bimolecular radical addition. Indicative of relatively efficient radical chains, iodide **4** was completely consumed, there were not large amounts of products resulting from hydrogen abstraction, and some of the ditin (typically half) remained at the end of the reaction. A preparative cyclization gave **5** in 41% isolated yield after chromatography.[14] In these reactions,

(11) See Table V of failed cyclizations in ref 10b.

(12) For example, iodoacetates are 100 times better atom donors to alkyl radicals than alkyl iodides. Curran, D. P.; Bosch, E.; Kaplan, J.; Newcomb, M. *J. Org. Chem.* **1989**, *54*, 1826–1831.

(13) After the completion of our experiments, Barth and O-Yang reported the concentration dependence for the cyclization of **4** (ref 8i). The reader is referred to this paper for a discussion of the competing bimolecular reactions and for the structures of the dimeric (and sometimes trimeric) products. Our results are in very good agreement with those of Barth and O-Yang, and we suspect that their reactions were warmed by irradiation.

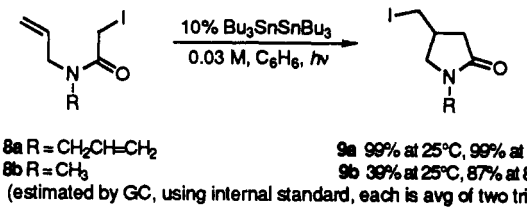


Figure 4.

the distance of the vessel from the lamp had no significant effect on the yield, although moving the lamp back did increase the reaction times. We also tried several experiments under the Jolly/Livinghouse conditions. When **4** was irradiated with 0.55 equiv of hexabutylditin and 3.5 equiv of propyl iodide (substituted for ethyl iodide to prevent evaporation), the same results were obtained at both 25 °C and 80 °C as with 10% ditin. The presence of the propyl iodide and the additional ditin had no effect, either beneficial or detrimental.

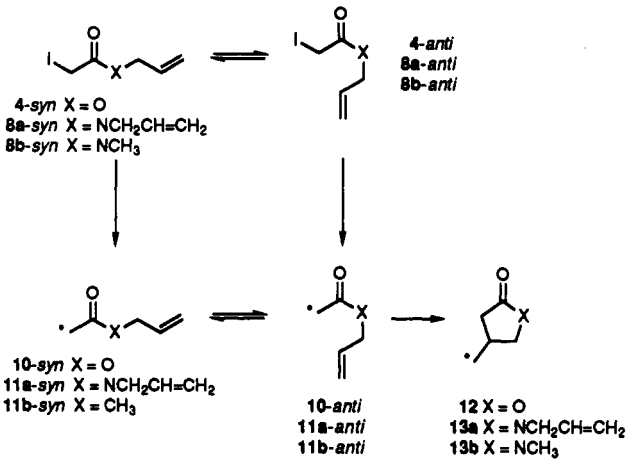
This powerful temperature effect also operates in a related system. We previously reported that the cyclization of **6** by the standard ditin procedure gave **7** in 55% yield (Figure 3). In this experiment, addition of excess ditin and prolonged irradiation were needed to reach this modest yield.[10b] A more careful reinvestigation revealed that the yield of **7** was highly dependent on the distance of the vessel from the sunlamp. Significant yields of **7** formed only when the sunlamp was very close (<6 cm) to the reaction. When the solution of **6** (0.03 M) was preheated to 80 °C and then irradiated, a rapid, reproducible reaction occurred and **7** was isolated in 83% yield. Again it was the heat, and not the light intensity, that improved the reaction.

Cyclizations of the iodoacetamides shown in Figure 4 also proved interesting. *N,N*-Diallyliodoacetamide (**8a**) cyclized rapidly (10–15 min) and in high yield whether the cyclization was conducted at 25 °C or 80 °C. The success of this reaction is striking in light of the difficulties with the ester **4**. In contrast, *N*-methyl-*N*-allyliodoacetamide (**8b**) gave much better results at 80 °C than at 25 °C. At 25 °C, **8b** showed the signs of a poor chain: we needed to add excess ditin to prevent the reaction from stopping, and it took 200 min for the yield of **9b** to reach 39%. At that time, 13% of unreacted **8b** still remained. At 80 °C, **8b** cyclized much more cleanly and rapidly (87% yield, <30 min).

We finally returned to the cyclization of the Jolly/Livinghouse iodide (Figure 1). Irradiation of **1** at 80 °C gave **2b** in 60–70% yield[15] whether the reaction was conducted under our standard conditions or with additional ditin and propyl iodide. At 25 °C, we obtained yields in the vicinity of 30% under either set of conditions. Thus, when temperature is strictly controlled, we find that the excess ditin and alkyl iodide additives have no effect.

On the basis of our results, we *speculate* that the observations of Jolly and Livinghouse were also due to temperature effects. The presence of large amounts of ditin and ethyl iodide[16] allowed the reaction to progress longer

Scheme I



without buildup of molecular iodine, and the mixture was warmed due to prolonged exposure to the sunlamp. As the temperature increased, the chains began to propagate.

Discussion

Although we have no accurate quantitative information, we believe that the temperature effects for cyclizations of these amides and esters are larger than those for normal radical cyclizations. The rate of cyclization of the hexenyl radical increases only by a factor of 5 on warming from 25 °C to 80 °C.[3] This seems too small to account for the dramatic differences in chain efficiency for these ester and amide substrates. Further, with the exception of **8a**, all the substrates respond to the temperature increase in a similar range, despite the fact that they must have widely different rates of cyclization.

Instead, we speculate that it is the rotation of the ester or amide bond that responds to temperature. The importance of this barrier in amide cyclizations has been recognized by Stork[7d] and by Ikida.[7e] The barriers to rotation in typical esters (~13 kcal/mol)[17] and amides (16–22 kcal/mol)[18] are significantly higher than activation energies for typical radical cyclizations (<10 kcal/mol).[3] In the range of 25–80 °C, more than 99% of **4** should be present as the syn rotamer **4a** (see Scheme I). Thus, when iodine is abstracted, radical **10** is born exclusively in the syn conformation (**10**-syn). However, **10**-syn is topologically prohibited from cyclizing, and at 25 °C, its lifetime is probably too short to surmount the barrier for ester bond rotation to **10**-anti. Thus, in the tin hydride reaction, direct reduction is observed, and in the atom-transfer reaction, chains will not propagate. At 80 °C, bond rotation is sufficiently rapid that **10**-syn can now isomerize (at least in part) to **10**-anti, and cyclization to **12** rapidly follows

(14) The structure of **5** was confirmed by ^1H and ^{13}C NMR and HRMS. Tin hydride reductive deiodination of **5** gave β-methyl-γ-butyrolactone. The product of 6-endo cyclization, δ-valerolactone, was not observed in the NMR spectrum of the reaction, and only a very small peak with the correct retention time for this product could be observed in the GC. We estimate that the exo/endo selectivity is >20/1.

(15) Experiments indicated that **2b** was not stable to heating under the reaction conditions, and that may account for the lower yield with this substrate. A GC–MS experiment indicated that three new products were formed, all with MW = 151. This corresponds to elimination of HI from **2b**. These products were not quantified or further identified.

(16) The beneficial effect of ethyl iodide is less clear; however, it is possible that it serves as a "radical buffer" if the chains are short relative to initiation. We assume that there is little selectivity in the initiation (be it photochemical C–I cleavage or iodine abstraction by $Bu_3Sn^\bullet$). Thus, in poorly propagating chains, reconversion of the product iodide to a radical will be a serious problem because eventually this radical will be lost by decomposition. Because iodine transfers are fast, an alkyl iodide can serve as a "radical buffer" by equilibrium exchange of the iodine. Thus with excess ethyl iodide, more often than not, it is the ethyl radical that decomposes, not the product radical. See: Castelhano, A. L.; Griller, D. *J. Am. Chem. Soc.* **1982**, *104*, 3655–3658. Newcomb, M.; Curran, D. P. *Acc. Chem. Res.* **1988**, *21*, 206–214. This effect should essentially disappear in effectively propagating chains with exothermic iodine transfers (but not necessarily with thermoneutral iodine transfers) because the product iodide will not be reconverted to a radical.

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(the barrier to cyclization may be lower than the barrier to return to **10**-syn).[19]

The amide cyclizations differ because radicals can be generated in a rotamer that is disposed to cyclize.[7d,e] For the symmetrical diallyl amide **8a**, the two rotamers of the radical are identical (**11a**-anti = **11a**-syn), and one of the allyl groups is always properly oriented for cyclization.[20] This substrate does not show the pronounced temperature dependence, but instead cyclizes efficiently at 25 °C and 80 °C. The *N*-methyl-*N*-allyl amide **8b** exists as a 52/48 mixture of rotamers **8b**-syn/**8b**-anti at room temperature. At 25 °C, **8b** shows an intermediate behavior between the behaviors of **4** and **8a**: it cyclizes to some extent (like **8a**), but the chains will not propagate efficiently (like **4**). Roughly half of the radicals are born in rotamer **11b**-anti, and these probably cyclize with good efficiency. Indeed the yield of cyclic product at 25 °C (39%) eventually approaches the rotamer population of **8b**-anti. However, fully half of the radicals are born in conformation **11b**-syn. These radicals cannot pass the barriers to **11b**-anti at room temperature, and they react by other pathways, thus breaking the chain. At 80 °C, isomerization of **11b**-syn to **11b**-anti becomes competitive, the chains propagate more efficiently, and the yield of cyclic products exceeds the starting rotamer population of **8b**-anti.

The analysis in Scheme I currently lacks any quantitative support; however, if it is correct, then the qualitative conclusions for preparative applications are clear. The efficiency of cyclization of amide-substituted radicals can be increased either by lowering the barrier to rotation or by increasing the percentage of the anti rotamer.[7d,e] Since esters exist exclusively in the syn conformation, the only recourse here is to lower the barrier to rotation. Changing solvents[21] or substituents can effect either the rotamer population or the barrier to rotation; however, temperature is an effective, easily altered variable. If an amide or ester radical cyclization reaction fails, heat it up.

Experimental Section[22]

Standard Cyclization Procedure: 4-Iodo-*cis*-hexahydro-2-coumaranone (7). A solution of cyclohex-2-en-1-yl iodoacetate (**6**) (1.06 g, 4.0 mmol) and hexbutylditin (0.2 mL, 0.4 mmol) in benzene (130 mL) was flushed with nitrogen and heated to 80 °C in a standard round-bottom flask. The reaction mixture was irradiated for 65 min with a 275-W sunlamp positioned above and to the side of the heating bath at a distance of 14 cm. After the mixture was cooled, tin compounds were removed by DBU workup.[10b] A solution of iodine (1 M) in ether was added to the reaction mixture until the color of I_2 just persisted (~0.4 mL). Next, wet ether (10 mL) and an ethereal solution of DBU (2 mL, 1 M) were added. The mixture was filtered through silica gel (8 g) in a 20-mm chromatography column eluting with ether (25 mL). After flash chromatography of the crude solid product with 3/1 hexanes/ethyl acetate, pure **7**[10b] was isolated as white crystals (880 mg, 83%): mp 97–99 °C; IR ($CDCl_3$) 2951, 2868, 2259, 2249, 1778, 1449, 1421, 1344, 1322, 1255, 1233, 1208, 1154, 1112, 1072, 1043, 1020, 985, 946, 925, 904 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) of mixture of diastereomers, assigned to major isomer (*exo*-iodide) δ 4.46 (q, *J* = 3.7 Hz, 1 H), 3.84 (ddd, *J* = 12.3, 10.7, 4.0 Hz, 1 H), 2.85 (quintet, *J* = 5.4 Hz, 1 H), 2.71 (dd, *J* = 17.3, 6.8 Hz, 1 H), 2.53 (d, *J* = 17.3 Hz, 1 H), 2.37 (m, 1 H), 2.24 (m, 1 H), 1.97 (m, 1 H), 1.68 (m, 1 H), 1.59–1.46 (m, 2 H), assigned to minor isomer (*endo*-iodide) δ 4.50 (dt, *J* = 10.5, 6.5 Hz, 1 H), 4.27 (dt, *J* = 12.8, 5.1, 1 H), 3.16 (m, 1 H), 2.67 (dd, *J* = 17.3, 13.1 Hz, 1 H), 2.55 (dd, *J* = 17.3, 8.2 Hz, 1 H), 2.37 (m, 1 H), 2.24 (m, 1 H), 1.97 (m, 1 H), 1.68 (m, 1 H), 1.43–1.21 (m, 2 H); ^{13}C NMR ($CDCl_3$) of mixture of diastereomers, assigned to major isomer (*exo*-iodide) δ 175.59, 78.91, 47.39, 38.63, 37.43, 29.73, 26.75, 21.98, assigned to minor isomer (*endo*-iodide) δ 174.10, 76.86, 43.71, 33.45, 33.29, 27.85, 23.91, 23.33; LRMS 266 (M^+); HRMS for $C_8H_{11}IO_2$ calcd 265.9804, found 265.9804.

N-Cyclohex-2-en-1-yl-N-methyliodoacetamide (1).[23]

N-Cyclohex-2-en-1-yltrichloroacetamide. Cyclohex-2-en-1-ol (4.9 g, 50 mmol) in ether (10 mL) was added dropwise to a stirred slurry of NaH (0.12 g, 5 mmol) in ether (30 mL) cooled in a methanol/ice bath. The resulting solution was added dropwise to trichloroacetonitrile (7.2 g, 50 mmol) in ether (10 mL) cooled in a methanol/ice bath. After the mixture was stirred at 25 °C for 15 min, the solvent was removed under reduced pressure, and the residue was vigorously shaken with pentane (75 mL) containing methanol (0.2 mL). The solution was filtered through a sintered-glass disk, and the dark solids were washed twice with pentane (25 mL). Removal of pentane under reduced pressure afforded the crude trichloroacetimidate (11.1 g, 92%) as pale yellow crystals. These were dissolved in xylenes (150 mL) and heated at reflux for 20 h. The cooled mixture was filtered through silica gel (35 g) eluting with toluene (125 mL), and the solvents were removed. The solid product was recrystallized from boiling hexanes (200 mL), and after concentration of the mother liquor to obtain a second crop of crystals, the total yield of pure title compound was 8.5 g (76% based on crude imidate): mp 86.0–86.5 °C; ^1H NMR ($CDCl_3$) δ 6.59 (s, 1 H), 5.97 (ddd, *J* = 9.9, 3.5, 1.5 Hz, 1 H), 5.63 (dd, *J* = 9.9, 2.3 Hz, 1 H), 4.45 (d, *J* = 2.3 Hz, 1 H), 2.06–1.93 (m, 3 H), 1.72–1.59 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 161.13, 132.73, 125.74, 92.81, 46.94, 28.63, 24.76, 19.45.

N-Cyclohex-2-en-1-yl-N-methyltrichloroacetamide. The *N*-cyclohex-2-en-1-yltrichloroacetamide (4.1 g, 17 mmol) was added portionwise to a stirred slurry of NaH (0.5 g, 21 mmol) in THF (40 mL) cooled in a methanol/ice bath. After the addition of 18-crown-6 (20 mg) and methyl iodide (1.5 mL, 24 mmol), the reaction mixture was stirred at 25 °C for 2.5 h and then heated to reflux for 20 h. The solvent was removed under reduced pressure, and the residue was shaken with ether (80 mL) and 1% aqueous HCl (60 mL). The aqueous layer was extracted with ether (3 × 30 mL). After the ether layer was washed with 5% aqueous $NaHCO_3$ (30 mL) and dried over $MgSO_4$, concentration under reduced pressure yielded the title compound (4.2 g, 97%) as a crystalline solid. This was used without purification in the next step, but a small analytical sample was prepared by flash chromatography using 9/1 hexanes/acetone: ^1H NMR ($CDCl_3$) major rotamer δ 5.98 (m, 1 H), 5.53 (m, 1 H), 5.13 (s, 1 H), 2.88 (s, 3 H), 2.04–1.63 (m, 6 H), minor rotamer δ 5.98 (m, 1 H), 5.53 (m, 1 H), 5.13 (s, 1 H), 3.19 (s, 3 H), 2.04–1.63 (m, 6 H); ^{13}C NMR ($CDCl_3$) major rotamer δ 160.60, 132.76, 126.75, 93.37, 56.14, 31.67, 26.44, 24.42, 21.29, minor rotamer δ 160.34, 132.62, 126.75, 93.78, 54.95, 32.93, 25.39, 24.42, 21.11.

N-Cyclohex-2-en-1-yl-N-methyliodoacetamide (1). The *N*-cyclohex-2-en-1-yl-*N*-methyltrichloroacetamide (4.2 g, 16 mmol) was heated to reflux with 6 M aqueous NaOH (90 mL) and 95% ethanol (90 mL) and then stirred at 25 °C for 3 days. The reaction mixture was extracted with ether (5 × 35 mL), and the extracts were acidified with 5 M methanolic HCl (50 mL). Water (40 mL) was added, and the organic solvents were removed under reduced pressure. The aqueous solution was washed with methylene chloride (3 × 20 mL) and then basified with solid KOH to pH ≈11. The amine, which separated as a light brown oil, was extracted into ether (5 × 25 mL), dried over Na_2SO_4, and concentrated under reduced pressure to a volume of 15 mL. Triethylamine (2.4 mL, 17 mmol) was added, and the solution was cooled in an ice bath. Chloroacetyl chloride (1.3 mL, 17 mmol)

(19) It is conceivable that cyclization could occur after the barrier is passed to C–O (or C–N) bond rotation, but before the anti conformer is reached.

(20) Although the radical and the double bond are proximate in the anti isomers, there must still be a barrier to cyclization. This barrier must consist (in part) of the energy required to rotate the OC–C• and OC–X bonds so that the preferred angle of attack (≈109°) can be reached.

(21) Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1989**, *111*, 5469–5470.

(22) IR spectra were obtained by using a neat film on NaCl plates except where indicated. For other general details, see refs 10a,b.

(23) This compound was made by minor modifications of standard literature procedures. (a) Trichloroacetimidate rearrangement: Clizbe, L. A.; Overman, L. E. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, pp 507–511. (b) N-Alkylation: Nordlander, J. E.; Catalane, D. B.; Eberlein, T. H.; Farkas, L. V.; Howe, R. S.; Stevens, R. M.; Tripoulas, N. A. *Tetrahedron Lett.* **1978**, 4987–4990.

in ether (15 mL) was added dropwise, and the reaction mixture was stirred at 25 °C for 4 h. The mixture was washed with H_2O (2 × 20 mL) and dried over $MgSO_4$, and the ether was removed under reduced pressure. The crude chloroacetamide was dissolved in anhydrous acetone (50 mL), and NaI (2.4 g, 16 mmol) was added. The flask was protected from light and the reaction mixture stirred at 25 °C for 4 h. After filtration to remove the solid NaCl and removal of the acetone, the residue was taken up in ether (25 mL), washed with H_2O (2 × 10 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the product was purifiifed by flash chromatography with 4/1 hexanes/acetone to yield the title compound (1.8 g, 40% based on the crude trichloroacetamide) as a pale yellow oil: IR 3455, 3023, 2935, 2863, 2837, 1721, 1630, 1476, 1447, 1400, 1386, 1352, 1340, 1316, 1251, 1231, 1149, 1068, 929, 898, 783, 727, 652, 615 cm^{-1}; ^1H NMR ($CDCl_3$) assigned to major rotamer δ 5.95 (m, 1 H), 5.37 (dq, J = 9.9, 1.9 Hz, 1 H), 5.14 (m, 1 H), 3.73 (s, 2 H), 2.86 (s, 3 H), 2.07–1.38 (m, 6 H), assigned to minor rotamer δ 5.95 (m, 1 H), 5.50 (dq, J = 10.2, 1.8 Hz, 1 H), 4.32 (m, 1 H), 3.77 (d, J = 2.3 Hz, 2 H), 2.76 (s, 3 H), 2.07–1.38 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 168.28, 167.93, 132.41, 132.18, 127.27, 126.91, 56.06, 50.98, 31.28, 29.02, 27.16, 25.75, 24.56, 24.33, 21.29, 21.13, -2.29, -3.59; LRMS 279 (M^+); HRMS for $C_9H_{14}INO$ calcd 279.0120, found 279.0120.

4-Iodo-1-methyl-*cis*-hexahydro-2-indolinone (2b). Standard cyclization of 1 afforded the title compound as a pale yellow oil (62% isolated yield after flash chromatography with 100% Et_2O): IR 3457, 2936, 2860, 1692, 1445, 1422, 1397, 1345, 1326, 1296, 1258, 1231, 1212, 1185, 1148, 1135, 1108, 1015, 979, 950, 937, 897, 869, 753, 700, 684, 651, 608, 564 cm^{-1}; ^1H NMR ($CDCl_3$) of mixture of diastereomers, assigned to major isomer (*exo*-iodide) δ 4.03 (ddd, J = 10.8, 9.0, 4.1 Hz, 1 H), 3.54 (q, J = 4.6 Hz, 1 H), 2.92 (m, 1 H), 2.74 (s, 3 H), 2.54–2.31 (m, 2 H), 2.25–1.09 (m, 6 H), assigned to minor isomer (*endo*-iodide) δ 4.31 (dt, J = 13.1, 5.0 Hz, 1 H), 3.42 (dt, J = 10.4, 6.2 Hz, 1 H), 2.82 (m, 1 H), 2.77 (s, 3 H), 2.54–2.31 (m, 2 H), 2.25–1.09 (m, 6 H); ^{13}C NMR ($CDCl_3$) of mixture of diastereomers δ 174.79, 172.94, 59.17, 58.55, 44.45, 41.31, 39.05, 36.91, 35.55, 34.20, 32.87, 28.11, 27.01, 26.79, 26.69, 25.59, 24.46, 22.03; LRMS 279 (M^+); HRMS for $C_9H_{14}INO$ calcd 279.0120, found 279.0120.

Allyl Iodoacetate (4). Acylation of allyl alcohol followed by halogen exchange (in a manner analogous to the preparation of 1) and purification by vacuum distillation provided the title compound (65% overall) as a colorless oil: bp 41.5–43.5 °C (0.35 mmHg); IR 3086, 3049, 3020, 2984, 2949, 2884, 1729, 1649, 1449, 1415, 1360, 1254, 1136, 1091, 989, 936 cm^{-1}; ^1H NMR (C_6D_6) δ 5.57 (m, 1 H), 5.00 (dq, J = 17.1, 1.5 Hz, 1 H), 4.91 (dd, J = 10.4, 1.5 Hz, 1 H), 4.25 (dt, J = 5.8, 1.3 Hz, 2 H), 3.04 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 168.51, 131.34, 119.07, 66.61, -5.66; LRMS 226 (M^+), 169, 141, 127, 99, 57, 43, 42, 41, 38.

β-(Iodomethyl)-γ-butyrolactone (5). Standard cyclization of 4 at 0.03 M afforded the title compound as a pale yellow oil (41% isolated yield after flash chromatography with 1/1 hexanes/ethyl acetate): IR 2962, 2907, 1851, 1770, 1477, 1429, 1415, 1381, 1344, 1321, 1250, 1231, 1171, 1090, 1075, 1016, 911, 876, 839, 732, 686 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.44 (dd, J = 9.4, 7.5 Hz, 1 H), 4.02 (dd, J = 9.4, 6.6 Hz, 1 H), 3.26 (dd, J = 10.3, 6.5 Hz, 1 H), 3.22 (dd, J = 10.3, 7.2 Hz, 1 H), 2.88 (septuplet, $J \approx 7$ Hz, 1 H), 2.70 (dd, J = 17.6, 8.5 Hz, 1 H), 2.35 (dd, J = 17.6, 7.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 175.57, 73.02, 37.30, 35.42, 6.71; HRMS for $C_5H_7IO_2$ calcd 225.9491, found 225.9492.

Cyclohex-2-en-1-yl Iodoacetate (6). Acylation of cyclohex-2-en-1-ol followed by halogen exchange (in a manner analogous to the preparation of 1) and purification by flash chromatography (19/1 hexanes/ethyl acetate) provided the title compound as a pale yellow oil (55%): IR 3032, 2941, 2868, 2834, 1724, 1415, 1266, 1159, 1140, 1087, 1050, 1008, 961, 910, 729, 639 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.00 (m, 1 H), 5.71 (dddd, J = 10.0, 3.6, 2.1, 1.8 Hz, 1 H), 5.28 (m, 1 H), 3.68 (dd, J = 11.6, 10.0 Hz, 2 H), 2.18–1.93 (m, 2 H), 1.93–1.57 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 168.54. 133.58, 124.75, 69.92, 27.88, 24.91, 18.70, -4.46; LRMS 266 (M^+); HRMS for $C_8H_{11}IO_2$ calcd 265.9804, found 265.9804.

***N*,*N*-Diallyliodoacetamide (8a).** Acylation of *N*,*N*-diallylamine followed by halogen exchange (in a manner analogous to the preparation of 1) and purification by flash chromatography (100% Et_2O) provided the title compound as a pale yellow oil (72%): IR 3082, 3011, 2983, 2920, 1650, 1448, 1409, 1283, 1190, 1097, 993, 926 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.88–5.73 (m, 2 H), 5.24–5.15 (m, 4 H), 3.98 (d, J = 5.7 Hz, 2 H), 3.92 (dt, J = 4.9, 1.0 Hz, 2 H), 3.71 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 168.19, 132.54, 132.28, 117.50, 117.08, 50.73, 48.33, -3.52; LRMS 265 (M^+); HRMS for $C_8H_{12}INO$ calcd 264.9964, found 264.9964.

***N*-Allyl-*N*-methyliodoacetamide (8b).** Acylation of *N*-methylallylamine followed by halogen exchange (in a manner analogous to the preparation of 1) and purification by flash chromatography (100% Et_2O) provided the title compound as a pale yellow oil (78%): IR 3081, 3039, 3009, 2982, 2930, 1638, 1476–1420, 1397, 1289, 1246, 1161, 1069, 991, 926, 742, 650 cm^{-1}; ^1H NMR ($CDCl_3$) assigned to major rotamer δ 5.77 (m, 1 H), 5.23–5.13 (m, 2 H), 3.95 (d, J = 5.8 Hz, 2 H), 3.73 (s, 2 H), 2.97 (s, 3 H), assigned to minor rotamer δ 5.77 (m, 1 H), 5.23–5.13 (m, 2 H), 3.92–3.91 (m, 2 H), 3.68 (s, 2 H), 2.90 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 168.14, 167.78, 132.54, 132.05, 131.49, 131.11, 117.50, 117.11, 53.59, 50.41, -3.23, -3.81; LRMS 239 (M^+); HRMS for $C_6H_{10}INO$ calcd 238.9807, found 238.9807.

1-Allyl-4-(iodomethyl)-2-pyrrolidinone (9a). Standard cyclization of **8a** afforded the title compound as a pale yellow oil (95% isolated yield after purification by flash chromatography with 100% Et_2O): IR 2979, 2917, 2861, 1688, 1489, 1443, 1418, 1269, 1189, 993, 927, 698, 617 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.70 (m, 1 H), 5.21 (s, 1 H), 5.17 (dd, J = 5.8, 1.2 Hz, 1 H), 3.87 (ddd, J = 16.8, 15.7, 6.2 Hz, 2 H), 3.47 (dd, J = 10.2, 7.7 Hz, 1 H), 3.27 (dd, J = 9.9, 5.7 Hz, 1 H), 3.18 (dd, J = 9.9, 7.4 Hz, 1 H), 3.06 (dd, J = 10.2, 6.1 Hz, 1 H), 2.73–2.54 (m, 2 H), 2.19 (dd, J = 15.7, 5.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 172.68, 132.05, 118.25, 52.99, 45.14, 38.59, 33.84, 9.70; LRMS 265 (M^+); HRMS for $C_8H_{12}INO$ calcd 264.9964, found 264.9964.

1-Methyl-4-(iodomethyl)-2-pyrrolidinone (9b). Standard cyclization of **8b** afforded the title compound as a pale yellow oil (67% isolated yield after purification by flash chromatography with 100% Et_2O): IR 3461, 2922, 2868, 1688, 1500, 1435, 1402, 1270, 1191, 1121, 996, 921, 731, 658 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.45 (dd, J = 10.1, 8.0 Hz, 1 H), 3.21 (dd, J = 9.9, 5.8 Hz, 1 H), 3.12 (dd, J = 9.9, 7.4 H, 1 H), 3.03 (dd, J = 10.1, 5.8 Hz, 1 H) 2.75 (s, 3 H), 2.57 (m, 1 H), 2.48 (dd, J = 16.5, 9.0 Hz, 1 H), 2.07 (dd, J = 16.5, 6.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 172.37, 54.96, 37.71, 32.90, 28.98, 10.13; LRMS 239 (M^+); HRMS for $C_6H_{10}INO$ calcd 238.9807, found 238.9807.

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Supplementary Material Available: Copies of ^{13}C and/or ^1H NMR spectra of all compounds in the Experimental Section (24 pages). Ordering information is given on any current masthead page.