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H- Transfer-Initiated Synthesis of γ -Lactams: Interpretation of Cycloisomerization and Hydrogenation Ratios

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Abstract

A cobaloxime/H₂ system used to synthesize valuable γ -lactams from acrylamide molecules is described. In addition to cycloisomerized lactams, linear hydrogenated products were also observed. The amounts of the hydrogenation product were observed to correlate with the bulk of the substituent on the acrylamide nitrogen. Further analysis of the product distributions with experimental and computational studies suggested that while cyclization can occur from one C=C acrylamide rotamer, hydrogenation can occur from both. This observation was further evinced through calculation of the hydrogenation rate constant, which was observed to be ca. 10² faster than previously determined for a related system using ⁿBu₃SnH.

Graphical Abstract

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Author Contributions

All authors have given approval to the final version of the manuscript.

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ASSOCIATED CONTENT

Supporting Information

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Synthesis and characterization (¹H and ¹³C NMR, mass spectrometry) of acrylamides and their reaction products, kinetic studies, DFT studies (PDF)

Cartesian Coordinates of DFT-Optimized Molecules (PDF)

Details of the X-ray crystal structure for 6-Ad-*cis* (CIF)

Details of the X-ray crystal structure for 6-Ad-*trans* (CIF)

Keywords

H· transfer; cobaloxime; γ -lactam; cycloisomerization; hydrogenation

The γ -lactam structure is found in many natural products^{1–3} and as a core component in a wide variety of pharmaceutically active compounds. Significant examples (Figure 1) include lenalidomide (Revlimid, Celgene),^{4,5} levetiracetam (Keppra, UCB pharmaceuticals),⁶ doxapram,³ and (–)-azaspirene⁷ or related derivatives of 2-pyrrolidinones (of which there are countless examples).^{8,9} Lenalidomide is an immunomodulatory drug which is used in the treatment of multiple myeloma and was ranked third in sales with \$9.685 billion¹⁰ for 2018, levetiracetam is an anticonvulsant used in the treatment of epilepsy,¹¹ doxapram is a chemoreceptor stimulant,¹² and (–)-azaspirene is a natural product derived from *Neosartorya sp.* that is an angiogenesis inhibitor.⁷ These examples alone show that the synthesis of γ -lactam-containing products is highly desirable in synthetic organic and medicinal chemistry settings.

Because of the prevalence of γ -lactam core structures, several complementary methodologies have been developed for their synthesis. Often, radical cyclization is used to prepare γ -lactams, with the cyclizing radical generated by the addition of an external radical ($R\cdot$,^{13–15} $ArCH_2\cdot$,¹⁶ $RCO_2F_2C\cdot$,¹⁷ or $RS\cdot$)¹⁸ to an acrylamide or *N*-allyl amide² double bond. Bu_3SnH can also generate relevant products, typically by reduction of aryl or alkyl halides.^{19–23} Significant advances in γ -lactam synthesis have been reported recently by C–H amidation²⁴ or with photoredox catalysis. In photoredox catalysis, cyclizing radicals can be generated from the reduction of aryl haMes,^{25,26} quinuclidine-mediated hydrogen atom transfer photocatalysis,^{27,28} proton-coupled electron-transfer to amidyl radicals,²⁹ or the application of photoactive flavin-based enzymes.³⁰ A conceptually related Co-catalyzed H-initiated olefin isomerization/cycloisomerization reaction has also recently been described.³¹

Our group has demonstrated the ability to generate radicals from appropriately substituted olefins by H· transfer from transition-metal hydrides ($CpCr(CO)_3H$,^{32,33} $HV(CO)_4(P-P)$ ($P-P$ = chelating phosphine ligand),³⁴ and $H_2/Co-(dmgBF_2)_2(THF)_2$ ($1/H_2$, dmg = dimethylglyoximate).^{35,36} In some cases, $CpCr(CO)_3H$ ³⁷ or **1** can be employed catalytically

(<10 mol %)³⁵ and regenerated with hydrogen gas. In addition to acrylate acceptors which were originally employed, we have also been successful in the catalytic transformation of enol ethers and enones using a **1**/H₂ system.^{35,38} Here, we report the cyclization of substituted acrylamides to γ -lactams catalytically by **1** and H₂. In addition to the desired γ -lactam products, we observe some hydrogenation that can be minimized by the addition of bulky *N*-substituents. We propose a mechanism to explain the cyclization/hydrogenation ratios that have been observed with a combination of experiments and density functional theory (DFT).

Acrylamides with varied *N*-substituted R groups can be prepared by reductive amination of an appropriate aldehyde and subsequent addition of acryloyl chloride.³⁹ Upon the reaction of acrylamides under 7.1 atm (90 psig) H₂ with **1** (analogous conditions as previously used for enone cyclization)³⁵ overnight, cycloisomerized γ -lactams produced. The product cycloisomerization (Scheme 1) is believed to result from the removal of an H $\cdot$ by Co $\cdot$ from the cyclized radical intermediate; such a reaction was previously observed for enones³⁵ (**1** remains largely in the Co(II) form even under substantial hydrogen pressure).

Table 1 shows the product distributions observed in the reaction of *N*-substituted acrylamides with cobaloxime **1**/H₂. For R = alkyl, the cycloisomerized product was observed (29–79% yield); these transformations always generated the terminal alkene (This product likely results because the methyl hydrogen of the cyclized radical is more accessible than the tertiary hydrogen as shown in Scheme 1). The cycloisomerization reactions gave both diastereomeric products (cis and trans). The ¹H NMR spectra of these diastereomers were in general resolvable, although they did not permit the identification of one diastereomer as cis and the other as trans. If we assume, however, that cyclization occurs through the C=N rotamer (**2**) pictured in Scheme 1 (which is Z for R = isopropyl (*i*Pr)), with both radical C–C rotamers (**4** and **5**) thermally accessible, we expect **4** to be lower in energy, and formation of the trans diastereomer to be favored.⁴⁰ We have therefore assumed that the more abundant diastereomer (the first in the parenthetical ratios in Table 1) is the trans one. In the case of R = adamantyl (Ad), we have been able to separate the diastereomers of the γ -lactam and to confirm by X-ray crystallography (Figure 2) that the more abundant diastereomer is, in fact, trans.

However, in many cases, as Table 1 shows, significant hydrogenation was also observed. Particularly large amounts of hydrogenation were observed with R = 1-naphthyl (79%, Np), *n*-hexyl (45%, *n*hex), 2-furylmethyl (45%), and Bn (44%) substituents on the acrylamide nitrogen, whereas cases with bulky substituents on nitrogen (e.g., *tert*-butyl and Ad) gave little hydrogenated product (12% and 11% respectively). No hydrogenation was observed when the nitrogen substituent was a bulky aryl group (Table 1).⁴¹

To explain the cyclization and hydrogenation ratios observed, the kinetics of Scheme 1 were examined. The ¹H NMR spectrum of each acrylamide shows signals for two conformational isomers. The **2**/**3** conformational interconversion rates were observed to be slow (in comparison with other rates measured or calculated here, vide infra) for the acrylamide. We estimate that when R = *i*Pr, the conformational interconversion rate is 67 s^{−1},⁴² which is corroborated by prior reports.^{43,44} Upon the reaction of **1** and H₂, a small amount (*K*_{eq} =

0.014(7) atm⁻¹)⁴⁵ of the putative^{45,46} “cobalt hydride” (**1H**) is formed in solution, which initiates the reaction. In the context of this experiment, the initial H· transfer was irreversible; the monodeuterated cycloisomerized product was observed in reaction of an acrylamide (R = Ad) with 7.1 atm D₂ (Figure S1).

Upon generation of the acrylamide radical species, cyclization or further hydrogenation can result. In a related study, Li and Curran concluded that acrylamide radical rotamers in the **9** (*E*) conformation are unable to cyclize.¹⁹ In this case, hydrogenation is expected. These acrylamide radicals also possess the potential to convert between the **4** and **9** (Figure 3) forms. Acrylamide radical rotamer interconversion rates are known to be faster than the parent acrylamide; this has been rationalized on the basis of cross-conjugation of the lone pair on the amide nitrogen with the vinyl group.^{44,47} With DFT, the radical conformational interconversion rate constants were calculated using transition-state theory.⁴⁸ For a subset of R groups, these rate constants were calculated to be 10²–10⁵ s⁻¹ (Table 2) and were found to be dependent, as expected on the basis of steric grounds, on the nature of the bulk of the acrylamide R substituent such that Ad > ^tBu » ⁱPr > Bn (^tBu = *tert*-butyl, Bn = benzyl).

For the molecules computationally studied, cyclization rate constants were observed to be at least 10² faster than the conformational interconversion rate constants. These cyclization rates were also calculated with transition-state theory;⁴⁸ similar methods have been successfully used to calculate cyclization rates for 5-*exo*⁴⁹ and 5-*endo-trig*⁵⁰ reactions (see SI for full experimental details). These computed rates (Table 2) span a range of 10⁶ – 10⁷ s⁻¹, which agrees with prior experimental work (10⁶ – 10⁸ s⁻¹).^{43,44}

The cyclization and conformational interconversion rates alone, however, do not explain product distributions. For instance, when R = ^tBu or Ad, the proportion of hydrogenation is greater than expected from the **2/3** conformational isomer ratios in the starting material. This observation implies that some hydrogenation is produced directly from **4** or **5** in addition to **9**.

To probe the hypothesis that hydrogenated product could occur from both **4/5** and **9**, an acrylamide substrate with R = ⁱPr was treated under different hydrogen pressures (9.2, 14.6, 21.4 atm), which, in turn, correspond to different **1H** concentrations in solution (*K*_{CoH} = 0.014(7) atm⁻¹).⁴⁵ These **1H** concentration values were observed to be linearly dependent on the hydrogenation to cycloisomerization ([**8**]: [**7**]) ratio observed, such that at higher pressures, significantly more hydrogenation is observed than cycloisomerization (Figure S3). Of note is that the *y*-intercept (which is expected to be zero) is a small negative number. This value is attributed primarily to uncertainty for the pressure measurement, which we estimate to be ±20 psig (from the gradations on pressure gauge).

The irreversible initial H· transfer suggests that **4** and **9** do not equilibrate before they can react further. From the Curtin-Hammett principle,⁵¹ the ratio of **4** and **9** is provided by eq 1. There, *k*_{H1} and *k*_{H2} are rate constants for the initial H· transfer and *K*₂₃ = [**2**]/[**3**]. If *k*_{H1} ≈ *k*_{H2}, the ratio of the radical intermediates [**4**]/[**9**] = *K*₂₃. Thus, the concentrations of the radicals are guided by *K*₂₃, not the equilibrium constant for **4** and **9**. This approximation also allows the estimation of *k*_{H3} by competition kinetics (see eq S3–S10 for derivation). In eq 2,

we have assumed that k_{H3} is approximately equal for the hydrogenation of **4** and **9** (Discussion S1). The cyclization rate constant (k_{cyc}) is provided from DFT calculations and $[2]/([2]+[3])$ is found experimentally. The slope of plot of $[8]/[7]$ against $[1H]$ (Figure S3) provides an estimate for k_{H3} as $4 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$. This estimated rate constant is fast, but not unreasonably so.

$$\frac{[4]}{[9]} = \frac{k_{H1}}{k_{H2}} K_{23} \quad (1)$$

$$\frac{[8]}{[7]} = \frac{k_{H3}[1H]}{k_{cyc}} \left(\frac{[3] + [2]}{[2]} \right) \quad (2)$$

We compared the rate constants estimated here with the $^n\text{Bu}_3\text{SnH}$ hydrogenation rate constant (analogous to k_{H3}) approximated by Curran et al. in their radical cyclization of α -halo-*ortho*-alkenyl anilides.⁵² In this work, Curran et al. approximate the hydrogenation rate of $^n\text{Bu}_3\text{SnH}$ (analogous to k_{H3}) to be $2 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$.^{52–54} This value is ca. 10^2 slower than k_{H3} found for the system reported here. In Curran's 6-*exo* cyclization, they found that a syringe pump was necessary to provide cyclized products—an observation in agreement with the slow cyclization rate found ($k_{cyc}(6\text{-exo}) = 8 \times 10^4 \text{ s}^{-1}$) in their study⁵². This is in contrast to the 5-*exo* cyclization (which cyclize ca. 10^2 faster than 6-*exo*, shown above) case found by Li and Curran,¹⁹ in which product cyclization and hydrogenation ratios exactly mirrored input *Z/E* conformations. Therefore, one might reasonably expect more hydrogenation if the **1H** system employed here were applied to slower radical cyclization reactions, such as the 6-*exo* previously discussed.⁵²

Collectively our experiments and calculations suggest the mechanism in Figure 3. $\text{H}\cdot$ transfer to the acrylamides **2** and **3** is irreversible, but its slowness, and the Curtin–Hammett principle suggest that acrylamide radicals **4** and **9** are formed in the ratio provided by eq 1. These rotamers undergo cyclization and hydrogenation more rapidly than they interconvert. Only **4** (and the small amount of **5**) can cyclize, whereas all the generated radical species can undergo hydrogenation.

The cobaloxime-catalyzed transfer of $\text{H}\cdot$ to acrylamides from H_2 offers an attractive alternative to reported methods of generating radicals for cyclization to γ -lactams. The reaction is particularly effective when radical cyclization is fast and a bulky substituent is on the amide nitrogen.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

- (1). Caruano J; Muccioli GG; Robiette R Biologically Active γ -Lactams: Synthesis and Natural Sources. *Org. Biomol. Chem.* 2016, 14, 10134–10156. [PubMed: 27748489]
- (2). Soleimani-Amiri S; Vessally E; Babazadeh M; Hosseinian A; Edjlali L Intramolecular Cyclization of N-allyl Propiolamides: A Facile Synthetic Route to Highly Substituted γ -lactams (a review). *RSC Adv.* 2017, 7, 28407–28418.
- (3). Ahankar H; Ramazani A; Iepokura K; Lis T; Joo SW Synthesis of Pyrrolidinone Derivatives from Aniline, an Aldehyde and Diethyl Acetylenedicarboxylate in an Ethanolic Citric Acid Solution Under Ultrasound Irradiation. *Green Chem.* 2016, 18, 3582–3593.
- (4). Chang X; Zhu Y; Shi C; Stewart AK Mechanism of Immunomodulatory Drugs' Action in the Treatment of Multiple Myeloma. *Acta Biochim. Biophys. Sin.* 2014, 46, 240–253. [PubMed: 24374776]
- (5). Qiu X; Sun N; Kong Y; Li Y; Yang X; Jiang B Chemoselective Synthesis of Lenalidomide-Based PROTAC Library Using Alkylation Reaction. *Org. Lett.* 2019, 21, 3838–3841. [PubMed: 31066567]
- (6). Martinez de Marigorta E; de los Santos JM; Ochoa de Retana AM; Vicario J; Palacios F Multicomponent Reactions in the Synthesis of γ -lactams. *Synthesis* 2018, 50, 4539–4554.
- (7). Hayashi Y; Shoji M; Yamaguchi J; Sato K; Yamaguchi S; Mukaiyama T; Sakai K; Asami Y; Kakeya H; Osada H Asymmetric Total Synthesis of (–)-Azaspiroene, A Novel Angiogenesis Inhibitor. *J. Am. Chem. Soc.* 2002, 124, 12078–9. [PubMed: 12371831]
- (8). Ye L-W; Shu C; Gagosz F Recent Progress Towards Transition Metal-Catalyzed Synthesis of γ -lactams. *Org. Biomol. Chem.* 2014, 12, 1833–1845. [PubMed: 24473105]
- (9). Yi W; Fang X-X; Liu Q-Y; Liu G-Q Metal-Free Synthesis of Oxazolidine-2,4-diones and 3,3-Disubstituted Oxindoles via ICl-Induced Cyclization. *Eur. J. Org. Chem.* 2018, 2018, 6671–6681.
- (10). McGrath NA; Brichacek M; Njardarson JT A Graphical Journey of Innovative Organic Architectures That Have Improved Our Lives. *J. Chem. Educ.* 2010, 87, 1348–1349.
- (11). Lyseng-Williamson KA Levetiracetam: A Review of its Use in Epilepsy. *Drugs* 2011, 71, 489–514. [PubMed: 21395360]
- (12). Golder FJ; Hewitt MM; McLeod JF Respiratory Stimulant Drugs in the Post-Operative Setting. *Respir. Physiol. Neurobiol.* 2013, 189, 395–402. [PubMed: 23791825]
- (13). Wang H; Guo L-N; Duan X-H Silver-catalyzed Oxidative Coupling/Cyclization of Acrylamides with 1,3-Dicarbonyl Compounds. *Chem. Commun.* 2013, 49, 10370–10372.
- (14). Zhao Y; Sharma N; Sharma UK; Li Z; Song G; Van der Eycken EV Microwave-Assisted Copper-Catalyzed Oxidative Cyclization of Acrylamides with Non-Activated Ketones. *Chem. - Eur. J* 2016, 22, 5878–5882. [PubMed: 26868308]
- (15). Guo L-N; Deng Z-Q; Wu Y; Hu J Transition-Metal Free Alkylarylation of Acrylamides Initiated by Radical C–C Bond Cleavage of the Tertiary Cycloalkanols. *RSC Adv.* 2016, 6, 27000–27003.
- (16). Zhou S-L; Guo L-N; Wang H; Duan X-H Copper- Catalyzed Oxidative Benzylarylation of Acrylamides by Benzylic C–H Bond Functionalization for the Synthesis of Oxindoles. *Chem. - Eur. J* 2013, 19, 12970–12973. [PubMed: 24038342]
- (17). Xia X-F; Zhu S-L; Li Y; Wang H Palladium-Catalyzed Radical Cascade Difluoroalkylation/ Cyclization of Acrylamide with Ethyl Difluorobromoacetate. *RSC Adv.* 2016, 6, 51703–51709.
- (18). Xia X-F; Zhu S-L; Wang D; Liang Y-M Sulfide and Sulfonyl Chloride as Sulfonylating Precursors for the Synthesis of Sulfone-Containing Isoquinolinonediols. *Adv. Synth. Catal.* 2017, 359, 859–865.
- (19). Li X; Curran DP Diverging Chemoselective Reactions of Separable Amide Rotational Isomers. *Org. Lett.* 2010, 12, 612–614. [PubMed: 20038129]

- (20). Stork G; Mah R Radical Cyclization of Allylic Haloacetamides a Route to cis-Fused Pyrrolidones and Piperidones. *Heterocycles* 1989, 28, 723–727.
- (21). Tamura O; Matsukida H; Toyao A; Takeda Y; Ishibashi H Is an Iodine Atom Almighty as a Leaving Group for Bu₃SnH-Mediated Radical Cyclization? The Effect of a Halogen Atom on the 5-endo-trig Radical Cyclization of N-vinyl- α -halo Amides. *J. Org. Chem.* 2002, 67, 5537–5545. [PubMed: 12153251]
- (22). Clark AJ; Curran DP; Fox DJ; Ghelfi F; Guy CS; Hay B; James N; Phillips JM; Roncaglia F; Sellars PB; Wilson P; Zhang H Axially Chiral Enamides: Substituent Effects, Rotation Barriers, and Implications for their Cyclization Reactions. *J. Org. Chem.* 2016, 81, 5547–5565. [PubMed: 27267662]
- (23). Rancourt J; Gorys V; Jolicoeur E Generation of Glyciny radicals *via* a 1,5-Hydrogen Atom Transfer Reaction. Applications to γ -lactam Formation. *Tetrahedron Lett.* 1998, 39, 5339–5342.
- (24). Hong SY; Park Y; Hwang Y; Kim YB; Baik M-H; Chang S Selective Formation of γ -lactams via C-H Amidation Enabled by Tailored Iridium Catalysts. *Science* 2018, 359, 1016–1021. [PubMed: 29496875]
- (25). Chen J-Q; Chang R; Lin J-B; Luo Y-C; Xu P-F Photoredox-Induced Intramolecular 1,5-H Transfer Reaction of Aryl Iodides for the Synthesis of Spirocyclic γ -Lactams. *Org. Lett.* 2018, 20, 2395–2398. [PubMed: 29613807]
- (26). Chen J-Q; Wei Y-L; Xu G-Q; Liang Y-M; Xu P-F Intramolecular 1,5-H Transfer Reaction of Aryl Iodides Through Visible-Light Photoredox Catalysis: A Concise Method for the Synthesis of Natural Product Scaffolds. *Chem. Commun.* 2016, 52, 6455–6458.
- (27). Ye J; Kalvet I; Schoenebeck F; Rovis T Direct α -Alkylation of Primary Aliphatic Amines Enabled by CO₂ and Electrostatics. *Nat. Chem* 2018, 10, 1037–1041. [PubMed: 30061617]
- (28). Yu W-L; Luo Y-C; Yan L; Liu D; Wang Z-Y; Xu P-F Dehydrogenative Silylation of Alkenes for the Synthesis of Substituted Allylsilanes by Photoredox, Hydrogen-Atom Transfer, and Cobalt Catalysis. *Angew. Chem. Int. Ed.* 2019, 58, 10941–10945.
- (29). Nguyen ST; Zhu Q; Knowles RR PCET-Enabled Olefin Hydroamidation Reactions with N-Alkyl Amides. *ACS Catal* 2019, 9, 4502–4507.
- (30). Biegasiewicz KF; Cooper SJ; Gao X; Oblinsky DG; Kim JH; Garfinkle SE; Joyce LA; Sandoval BA; Scholes GD; Hyster TK Photoexcitation of Flavoenzymes Enables a Stereoselective Radical Cyclization. *Science* 2019, 364, 1166–1169. [PubMed: 31221855]
- (31). Crossley SWM; Barabé F; Shenvi RA Simple, Chemoselective, Catalytic Olefin Isomerization. *J. Am. Chem. Soc.* 2014, 136, 16788–91. [PubMed: 25398144]
- (32). Smith DM; Pulling ME; Norton JR Tin-free and Catalytic Radical Cyclizations. *J. Am. Chem. Soc.* 2007, 129, 770–771. [PubMed: 17243807]
- (33). Hartung J; Pulling ME; Smith DM; Yang DX; Norton JR Initiating Radical Cyclizations by H-Transfer from Transition Metals. *Tetrahedron* 2008, 64, 11822–11830.
- (34). Choi J; Pulling ME; Smith DM; Norton JR Unusually Weak Metal-Hydrogen Bonds in HV(CO)₄(P-P) and Their Effectiveness as H- Donors. *J. Am. Chem. Soc.* 2008, 130, 4250–4252. [PubMed: 18335937]
- (35). Li G; Han A; Pulling ME; Estes DP; Norton JR Evidence for Formation of a Co–H Bond from (H₂O)₂Co(dmgbF₂)₂ under H₂: Application to Radical Cyclizations. *J. Am. Chem. Soc.* 2012, 134, 14662–14665. [PubMed: 22897586]
- (36). Li G; Kuo JL; Han A; Abuyuan JM; Young LC; Norton JR; Palmer JH Radical Isomerization and Cycloisomerization Initiated by H- Transfer. *J. Am. Chem. Soc.* 2016, 138, 7698–7704. [PubMed: 27167594]
- (37). Yao C; Dahmen T; Gansauer A; Norton J Anti- Markovnikov Alcohols via Epoxide Hydrogenation Through Cooperative Catalysis. *Science* 2019, 364, 764–767. [PubMed: 31123133]
- (38). Kuo JL; Hartung J; Han A; Norton JR Direct Generation of Oxygen-Stabilized Radicals by H-transfer from Transition Metal Hydrides. *J. Am. Chem. Soc.* 2015, 137, 1036–1039. [PubMed: 25569214]
- (39). Full details of the procedure for their synthesis and characterization are in the SI.
- (40). A DFT calculation with R = iPr showed that 4 was lower in energy than 5 by 4.86 kcal mol^{–1}.¹

- (41). The remaining substrate in these reactions was unreacted and recovered during purification. The reaction was not optimized. We believed that no hydrogenation product was observed when R = aryl because the ratio of 2/3 heavily favors 2.
- (42). Measured from line-broadening in the room-temperature NMR spectrum.
- (43). Musa OM; Choi S-Y; Horner JH; Newcomb M Absolute Rate Constants for α -Amide Radical Reactions. *J. Org. Chem.* 1998, 63, 786–793. [PubMed: 11672074]
- (44). Musa OM; Horner JH; Newcomb M Laser Flash Photolysis Measurements of the Kinetics of Carbon-Nitrogen Bond Rotations in α -Amide Radicals. *J. Org. Chem.* 1999, 64, 1022–1025. [PubMed: 11674180]
- (45). Estes DP; Grills DC; Norton JR The Reaction of Cobaloximes with Hydrogen: Products and Thermodynamics. *J. Am. Chem. Soc.* 2014, 136, 17362–17365. [PubMed: 25427140]
- (46). Lacy DC; Roberts GM; Peters JC The Cobalt Hydride that Never Was: Revisiting Schrauzer's "Hydridocobaloxime". *J. Am. Chem. Soc.* 2015, 137, 4860–4864. [PubMed: 25798900]
- (47). Curran DP; Guthrie DB; Geib SJ How Do Analogous α -Chloroenamides and α -Iodoenamides Give Different Product Distributions in 5-*endo* Radical Cyclizations? *J. Am. Chem. Soc.* 2008, 130, 8437–8445. [PubMed: 18540600]
- (48). McQuarrie DA; Simon JD 28–8. Transition-state Theory can be Used to Estimate Reaction Rate Constants Physical Chemistry: A Molecular Approach; University Science Books: Sausalito, CA, 1997; pp 1165–1169.
- (49). Guan X; Phillips DL; Yang D A Density Functional Theory Study of the 5-*exo* Cyclization Reactions of α -Substituted 6,6-Diphenyl-5-hexenyl Radicals. *J. Org. Chem.* 2006, 71, 1984–1988. [PubMed: 16496984]
- (50). Chatgililoglu C; Ferreri C; Guerra M; Timokhin V; Froudakis G; Gimisis T 5-*Endo-trig* Radical Cyclizations: Dis- favored or Favored Processes? *J. Am. Chem. Soc.* 2002, 124, 10765–10772. [PubMed: 12207532]
- (51). Seeman JI Effect of Conformational Change on Reactivity in Organic Chemistry. Evaluations, Applications, and Extensions of Curtin-Hammett Winstein-Holness Kinetics. *Chem. Rev.* 1983, 83, 83–134.
- (52). Guthrie DB; Geib SJ; Curran DP Synthesis of Highly Enantioenriched 3,4-Dihydroquinolin-2-ones by 6-*Exo-trig* Radical Cyclizations of Axially Chiral α -Halo-*ortho*-alkenyl Anilides. *J. Am. Chem. Soc.* 2009, 131, 15492–15500. [PubMed: 19799432]
- (53). Chatgililoglu C; Dickhaut J; Giese B Rate Constants and Arrhenius Parameters for the Reactions of Some Carbon-Centered Radicals with Tris(trimethylsilyl)silane. *J. Org. Chem.* 1991, 56, 6399–6403.
- (54). Chatgililoglu C; Ingold KU; Scaiano JC Rate Constants and Arrhenius Parameters for the Reactions of Primary, Secondary, and Tertiary Alkyl Radicals with Tri-*n*-butyltin Hydride. *J. Am. Chem. Soc.* 1981, 103, 7739–7742.

Figure 1.
Selected examples of pharmaceuticals and natural products containing a γ -lactam core.

Figure 2. Thermal ellipsoid representation of the molecular structure of (A) 3,4-*trans*- and (B) 3,4-*cis*-1-(adamantan-1-yl)-3-methyl-4-vinylpyrrolidin-2-one (50% probability ellipsoids). Hydrogen atoms and the disorder present in panel B are not shown. Details regarding the crystal structure refinement are set forth in the SI.

Figure 3.
Proposed reaction kinetics and mechanism.

Origin of cis/trans Products

Origin of Cycloisomerization

Scheme 1.
Product Origin and Distribution (R = Aryl or Alkyl)

Table 1.

Substrate Scope and Yields of Cycloisomerization and Hydrogenation

R	7 yield % (d.r.) ^a	8 yield % ^a
^t Pr	64 (3:1)	29
^t Bu	74 (4:1)	12
Ad	79 (4:1)	11
Bn	43 (3:1)	44
1-naphthyl	9	79
2-furylmethyl	42 (2.6:1)	45
<i>n</i> -hexyl	29	45
2,6-diethylphenyl	23	not observed
2,6-diisopropylphenyl	27	not observed
2,5-di- <i>tert</i> -butylphenyl	60	not observed

^a Isolated yields.

Table 2.

Starting Material 2/3 Ratio and Calculated Conformational Interconversion and Cyclization Rate Constants for Selected Acrylamide Radicals (s⁻¹)

R substituent	2/3 ratio^a	conformational interconversion rate for 4/9^b	cyclization rate^b
<i>i</i> Pr	69/31	3.1×10^2	2.0×10^6
<i>t</i> Bu	95/5	5.5×10^4	5.6×10^7
Ad	95/5	1.0×10^5	3.9×10^7
Bn	58/42	1.1×10^2	1.9×10^6

^aExperimentally determined ratio from ¹H NMR spectroscopy in the starting material

^bCalculated using transition-state theory with DFT

see Supporting Information for computational details.