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Selective Approach toward Multifunctionalized Lactams by Lewis Acid Promoted PhSe Group Transfer Radical Cyclization

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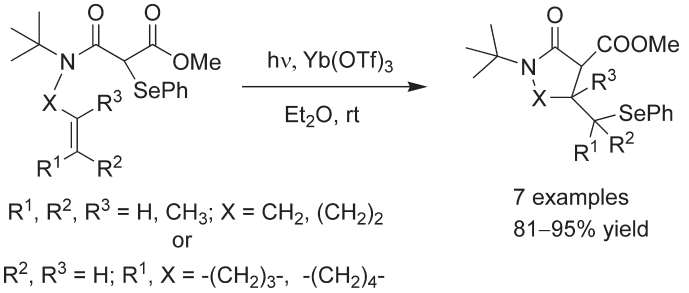
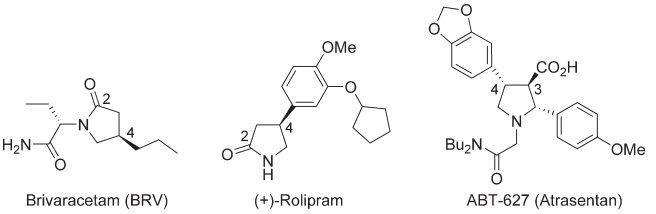


We have developed a regiospecific and highly stereoselective strategy for constructing the five-/six-membered monocyclic and bicyclic nitrogen heterocycle skeletons using PhSe group transfer radical cyclization of α-phenylseleno amido esters promoted by a Lewis acid (e.g., $Yb(OTf)_3$) under UV irradiation. We obtained 5-/6-*exo-trig* mode cyclization products for the *N*-allyl/homoallyl substrates, whereas the enamide substrate gave 5-*endo-trig* ring closure.

Introduction

Multifunctionalized five- and six-membered nitrogen heterocyclic skeletons are common in biologically active natural products and pharmaceutically relevant molecules.[1] In particular, 4-alkyl-2-pyrrolidinones, 4-alkylpyrrolidine-3-carboxylic acids, and 4-alkyl-2-pyrrolidinone-3-carboxylic acids form the core structures of many biologically significant compounds, for example, the antiepileptic drug brivaracetam (BRV),[2] the phosphodiesterase (PDE4) inhibitor rolipram,[3] and the endothelin antagonist ABT-627 (atrasentan).[4] Therefore, efficient and selective methods for the construction of highly functionalized pyrrolidines/pyrrolidinones, the key intermediates, have deservedly attracted much attention in research.[5]



Radical cyclization method is a general strategy used for building up cyclic compounds.[6] Atom or group transfer radical cyclization reactions, which involve the transfer of

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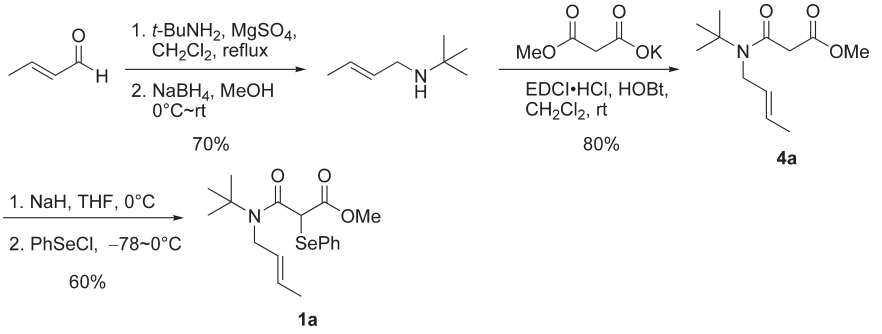
SCHEME 1. Synthesis of Cyclization Precursor 1a

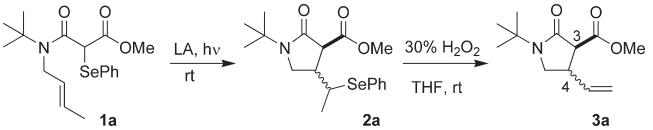


a halogen atom (X = I, Br, or Cl) or an aryl chalcogen group (X = SePh, or TePh) from one carbon center to another with concomitant C−C bond formation, are particularly effective for cyclic skeleton construction.[7] This approach is popular in organic synthesis since the halogen atom or chalcogen group retained in the product readily allows further functionalization.[8] In previous studies, we have demonstrated the possibility of enantioselective synthesis of carbocycles by bromo atom or PhSe group transfer radical cyclization of unsaturated β-keto esters catalyzed by chiral Lewis acids.[9] Very recently, we reported a photoinduced PhSe group transfer radical cyclization of *N*-alkenyl β-keto amides and its application in the formal synthesis of (±)-isocynometrine.[10] We report herein regiospecific and stereoselective synthesis of highly functionalized γ- and δ-lactams by exploiting Lewis acid promoted PhSe group transfer radical cyclization with amido esters as precursors.

Results and Discussion

Screening of Reaction Conditions. A PhSe group transfer radical cyclization precursor, amido ester **1a**, was synthesized as shown in Scheme 1. Since the steric bulkiness of substituents on the nitrogen atom of the tertiary amides significantly affects the cyclization efficiency,[10,11] bulky *tert*-butyl group was selected as the substituent on the nitrogen atom of the substrates. On one hand, the *tert*-butyl group locks the substrate in a conformation prone to cyclization; on the other hand, it can be readily removed by treatment with Lewis acid $Sc(OTf)_3$,[12] which is advantageous in syntheses of various substituted heterocycles.

TABLE 1. Effect of Lewis Acids on the PhSe Group Transfer Radical Cyclization of 1a



entry	Lewis acid (equiv)	initiating condition	solvent	time (h)	yield (%)[a] of **2a** (*trans*/*cis*)[b]
1	$Yb(OTf)_3$ (1)		Et_2O	16	
2		*hν*	Et_2O	16	64[c] (8.1:1)
3	$Yb(OTf)_3$ (1)	*hν*	Et_2O	2	85 (7.5:1)
4	$Yb(OTf)_3$ (0.3)	*hν*	Et_2O	2	71 (6.8:1)
5[d]	$Yb(OTf)_3$ (0.3)	*hν*	Et_2O	6	71[e] (7.5:1)
6	$Sc(OTf)_3$ (1)	*hν*	Et_2O	2	83 (7.3:1)
7	$Sm(OTf)_3$ (1)	*hν*	Et_2O	2	76 (8.0:1)
8	$Cu(OTf)_2$ (1)	*hν*	Et_2O	4	< 5
9	$Mg(ClO_4)_2$ (1)	*hν*	Et_2O	5	< 5
10	$Mg(ClO_4)_2$ (1)	*hν*	CH_2Cl_2	5	68 (11.3:1)

[a]Isolated yield. [b]The ratio of *trans*/*cis* isomers was determined by the crude ^1H NMR analysis of **3a**. [c]Including 8% oxidative elimination product **3a**. [d]Reaction at −45 °C. [e]Including 10% oxidative elimination product **3a**.

The results of the cyclization of the amido ester substrate **1a** under various reaction conditions are summarized in Table 1. Without UV irradiation, no reaction occurred even in the presence of 1 equiv of Lewis acid $Yb(OTf)_3$ after 16 h (entry 1). However, when the substrate was irradiated by UV light in the absence of $Yb(OTf)_3$, a 64% total yield of cyclized products, including 5-*exo* product **2a** (56%) and oxidative elimination product **3a** (8%), was obtained (entry 2). These results suggest that the photoinduced PhSe group transfer cyclization of α-phenylseleno amido ester proceeds via a radical pathway. The ^1H NMR analysis of the oxidative elimination product **3a** revealed that the dominant isomer of 5-*exo* product **2a** had a *trans* relationship of the 3-ester group and 4-alkyl group. In the presence of 1 equiv of $Yb(OTf)_3$, cyclized product **2a** could be obtained in 85% yield by initiating the radical reaction through UV irradiation, and the reaction time was shortened to 2 h (entry 3). When the amount of Lewis acid was reduced to 0.3 equiv, 71% yield was achieved (entry 4). This clearly indicates that Lewis acids may play an important role in accelerating the radical cyclization. However, the ratio of *trans*/*cis* isomers of **2a** remained at close range from 6.8 to 8.1 (entries 2−4), regardless of the addition of Lewis acid. This indicates that Lewis acid affects little if any on the stereoselectivity of the cyclization step. We also tried to increase the stereoselectivity

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(8) (a) Jolly, R. S.; Livinghouse, *J. Am. Chem. Soc.* **1988**, *110*, 7536. (b) De Buyck, L.; Cagnoli, R.; Ghelfi, F.; Merighi, G.; Mucci, A.; Pagnoni, U. M.; Parsons, A. F. *Synthesis* **2004**, 1680. (c) Helliwell, M.; Fengas, D.; Knight, C. K.; Parker, J.; Quayle, P.; Raftery, J.; Richards, S. N. *Tetrahedron Lett.* **2005**, *46*, 7129. (d) Chapelon, A.-S.; Ollivier, C.; Santelli, M. *Tetrahedron Lett.* **2006**, *47*, 2747. (e) Edlin, C. D.; Faulkner, J.; Helliwell, M.; Knight, C. K.; Parker, J.; Quayle, P.; Raftery, J. *Tetrahedron* **2006**, *62*, 3004.

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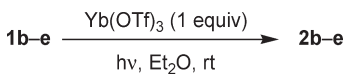
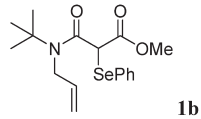
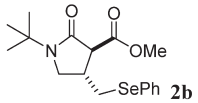
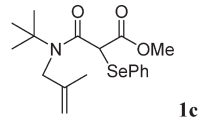
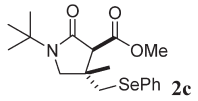
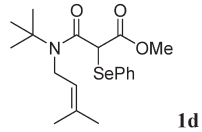
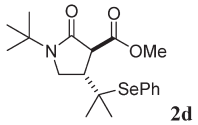
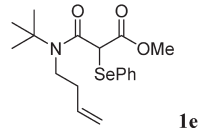
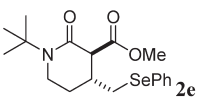
TABLE 2. Lewis Acid-promoted PhSe Group Transfer Radical Cyclizations of Compounds 1b−e[a]



entry	substrates	products	yield[b] (%) (*trans*:*cis*)[c]
1	 **1b**	 **2b**	85 (13.4:1)
2	 **1c**	 **2c**	95 (2.2:1)
3[d]	 **1d**	 **2d**	95
4	 **1e**	 **2e**	83

[a]Unless otherwise indicated, reaction time was 2 h. [b]Isolated yield. [c]Determined by ^{1}H NMR analysis of **2**. [d]Reaction time was 1.5 h.

of the cyclization by lowering down the reaction temperature. Substrate **1a** was irradiated for 6 h at −45 °C by UV light in the presence of 0.3 equiv of $Yb(OTf)_3$. A mixture of 5-*exo* product **2a** and oxidative elimination product **3a** was obtained in 71% combined yield, but the *trans*/*cis* ratio of **2a** (7.5:1) was not significantly increased compared with the result at room temperature (entry 5 vs entry 4). Other Lewis acids have also been screened (entries 6−10). In the presence of 1 equiv of $Sc(OTf)_3$ and $Sm(OTf)_3$ (two kinds of strong Lewis acids[13]), 83% and 76% yields were achieved, respectively, with the ratios of *trans*/*cis* isomers being 7.3:1 and 8.0:1, respectively (entries 6 and 7). However, in the presence of $Cu(OTf)_2$, a weaker Lewis acid, low conversion was observed (entry 8). In the case of $Mg(ClO_4)_2$, the solvents used seemed to have a key impact on the reaction outcomes. Specifically, no cyclized product was obtained in Et_2O (entry 9), whereas 68% yield and a higher *trans*/*cis* ratio (11.3:1) were achieved in CH_2Cl_2, with the reaction time being extended to 5 h (entry 10).[6f,14] Here, the solvent effect may be accounted for by the fact that $Mg(ClO_4)_2$ dissolves much better in CH_2Cl_2 than in Et_2O.

Then various types of *N*-alkenyl α-phenylseleno amido ester substrates (including the allyl-type substrates **1b−d**, the homoallyl substrate **1e**, the allyl type substrates **1f−g** containing a double bond being part of the carbocycles, and enamine compound **1h**) were prepared[15] and subjected to the above optimized cyclization conditions.

***N*-Allyl and Homoallyl Type Substrates 1b−e.** Similar to compound **1a**, compounds **1b−d** are *N*-allyl-type substrates but have different substitution patterns on the C=C double bond. By subjecting **1b−d** to the optimized condition for the PhSe group transfer radical cyclization, high yields of 5-*exo*-cyclization from 85 to 95% were achieved (Table 2, entries 1−3). Excellent stereoselectivities were observed for the cyclization of **1b** and **1d**; however, the ratio of *trans*/*cis* isomers was 2.2:1 for **1c**. As for the *N*-homoallyl-type substrate **1e**, 6-*exo* product **2e** was produced in 83% yield as a single stereoisomer (Table 2, entry 4). The structures of the cyclization products **2b−e** were determined by NMR experiments and were further confirmed by the structural analysis of **3b**, **3c**, **3e** (the reductive dephenylselenation products of **2b**, **2c**, **2e**, respectively), and **3d** (the oxidative elimination product of **2d**).[15]

The above results have revealed some interesting features which aid our understanding of the factors governing the outcome of the PhSe group transfer radical cyclization reactions of interest.

First of all, the above radical cyclization reactions are promoted by Lewis acid $Yb(OTf)_3$, similar to our previous report on PhSe group transfer radical cyclization of β-keto amides.[16] The 1,3-dicarbonyl groups of the amido ester substrates can chelate to strong Lewis acid like $Yb(OTf)_3$ in a bidentate fashion, which makes the α-radical intermediates generated from the cleavage of C−Se bond by photolysis even more electrophilic. As a result, the ring-closure step is accelerated through the addition of more electron-deficient α-radicals toward unactivated olefins. In addition, the PhSe group transfer step may also be accelerated in the presence of Lewis acid.[16] Therefore, the chelation of the β-dicarbonyl moiety of amido ester substrates to strong Lewis acids results in the rate acceleration for the cylization reactions. Convenient structural modifications of the multiple functionalized cyclization products render this method applicable to the synthesis of *N*-heterocyclic natural products. For example, the methoxycarbonyl group of the cyclization products can be removed to afford β-substituted γ-lactams following a literature procedure.[17]

Second, the cyclization reactions of amido esters **1a−e** are exclusively in *exo*-mode, which is independent of C=C double bond substitution patterns. However, in our previous studies, *endo*-cyclization products were obtained for the cyclization of β-keto amides **I**, analogous of the amido ester **1b**, under UV irradiation in the presence of Lewis acids (eq 1).[18] This difference may be attributed to distinct products formed from the two classes of substrates. *N*-Heterocycles were produced by Lewis acid-promoted PhSe group transfer radical cyclization of amido ester substrates,

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(14) For the improvement of stereoselectivity in some free-radical transformations by magnesium-based Lewis acids, see: (a) Guérin, B.; Ogilvie, W. W.; Guindon, Y. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; and references cited therein. (b) Dakterniuks, D.; Perchyonok, V. T.; Schiesser, C. H. *Tetrahedron: Asymmetry* **2003**, *14*, 3057.

(15) For details, see the Supporting Information.

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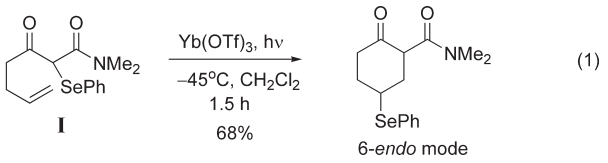
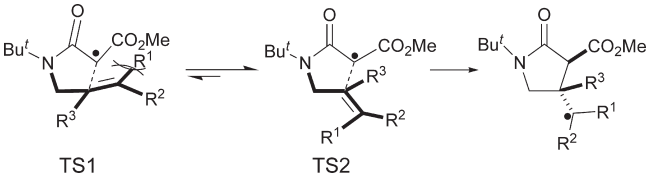
while carbocycles were obtained from the β-keto amide substrates.



(1)

The regioselectivity (5-*exo* vs 6-*endo*) of the cyclization of δ-unsaturated carbon-centered radicals have been well investigated in literature by theoretical calculations as well as experimental studies.[19−24] Julia reported that the regioselectivity of δ-unsaturated alkyl radicals forming either five- or six-membered carbocycles from the same precursor can be controlled by kinetic or thermodynamic factors.[20] Cyclization of 3-aza-5-hexenyl and 3-aza-5-methyl-5-hexenyl radicals revealed that 5-*exo* mode is preferred over 6-*endo* one.[21,22] Beckwith and Houk attributed the fact that the 3-aza systems, with a large group on nitrogen atom, produce exclusively *exo* product, regardless of substituents of the double bond, to the increased stereoelectronic effect due to the shorter C−N bonds with respect to C−C bonds.[20] The same outcome (5-*exo* cyclization) was observed in Ueno−Stork reactions which employ 3-oxa-5-hexenyl radical as the substrate.[23] Renaud reported that a highly stereoselective Ueno−Stork reaction was observed in which the acetal center was the unique stereogenic element, and δ-unsaturated carbon-centered radicals, either unactivated or stabilized by electron-withdrawing carbonyl groups, provided 5-*exo* mode cyclization.[24] Our observed 5-*exo* cyclization of *N*-allyl-type substrates **1a**−**d** seemed consistent with the above examples of constructing heterocycles by radical cyclizations.

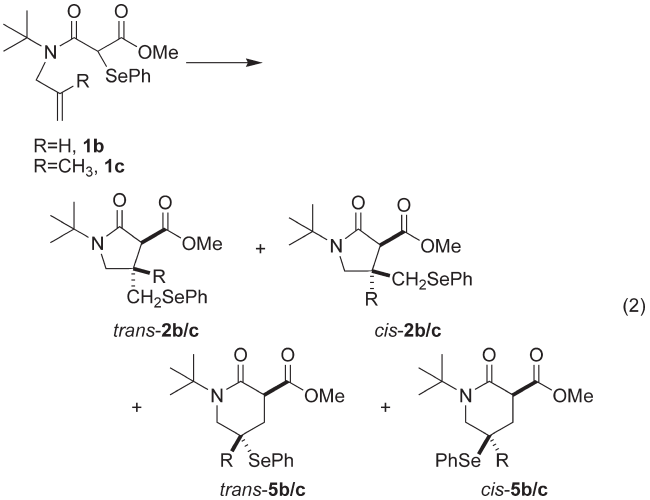
SCHEME 2. Stereoselectivities of Radical Cyclization of 1a−d



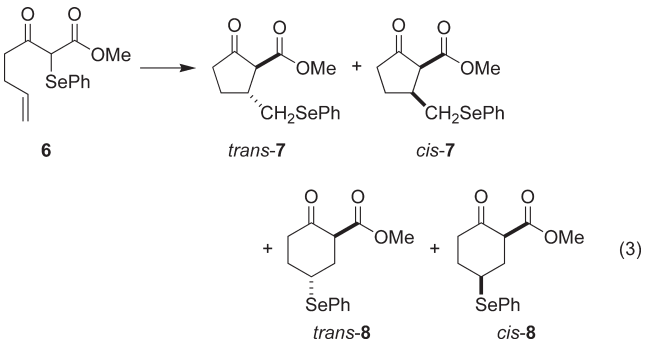
Third, in terms of stereoselectivity, the PhSe group transfer radical cyclization of substrates **1a**−**e** gave *trans* products as the major stereoisomers. In particular, high to excellent stereoselectivities were obtained for the PhSe group transfer radical cyclization of substrates **1a**−**b** and **1d**−**e**. A plausible explanation for the stereoselectivity of PhSe group transfer radical cyclization (5-*exo* mode closure, for example) is depicted in Scheme 2. For the substrates (**1a**−**b** and **1d**) with R^3 group being hydrogen atom (Scheme 2), transition state **2** (TS2) would be much favored over TS1 because of less steric interaction, resulting in a cyclization product having a *trans* configuration between 3-ester group and 4-alkyl group of 2-pyrrolidinones under kinetic control condition.

In contrast, for substrate **1c**, the R^3 is a methyl group and the R^1 and R^2 are both protons. Both the methyl group (R^3) and the methylene group (=CR^1R^2) are sterically hindered to a similar extent with respect to the ester group. As a result, TS1 and TS2 would be similar in energy and poor stereoselectivity is expected under kinetic control.

While it is not obvious whether the radical cyclization of **1a**−**d** proceeded through kinetic or thermodynamic control, we have carried out density function calculations on the thermodynamic stabilities of possible cyclization products for radical reactions of compounds **1b**, **1c**, and **6**, a model compound of **I**, using the Gaussian 03 program (eqs 2 and 3).[25]



(2)



(3)

All of the cyclization products were full optimized by B3LYP/6-31G(d) method without any restriction.

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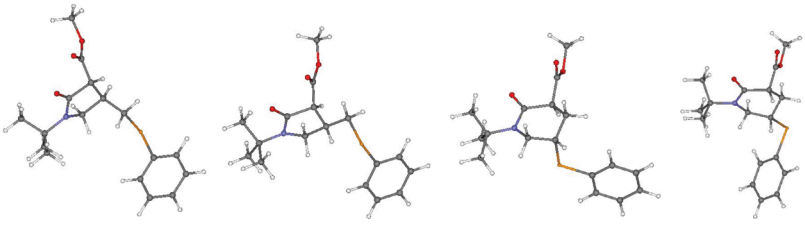

FIGURE 1. Calculated structures (*trans*/*cis*-**2b** and *trans*/*cis*-**5b**) and relative energies (kcal/mol) in Et_2O and in vacuum (in parentheses).

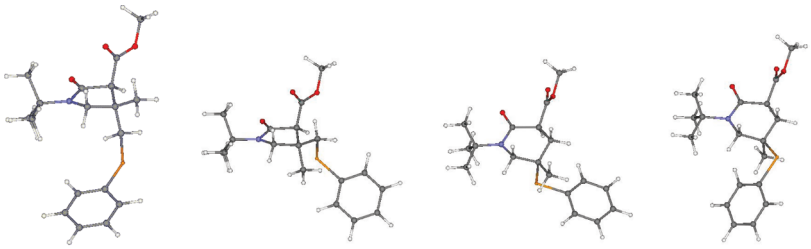

FIGURE 2. Calculated structures (*trans*/*cis*-**2c** and *trans*/*cis*-**5c**) and relative energies (kcal/mol) in Et_2O and in vacuum (in parentheses).

And harmonic vibration frequency calculations were also performed to ensure each structure being a minimum by using B3LYP/6-31G(d) method. Solvent effect in Et_2O and CH_2Cl_2 was evaluated by PCM model.[26] The relative free energies were calculated on the basis of the B3LYP/6-31G(d) energies with the thermal, entropy, and solvent energy corrections (eq 4).

$$\Delta G = \Delta E(\text{B3LYP}) + \text{enthalpy corrections} - T\Delta S \quad (4)$$

The calculation results (Figures 1−3) support our experimental data. The relative energies shown in Figure 1 reveal that the 5-*exo* cyclization products *trans*/*cis*-**2b** are much more stable than the 6-*endo* ones (*trans*/*cis*-**5b**) in Et_2O as well as in a vacuum, and *trans*-**2b** is more favorable than *cis*-**2b**. The same trend is found for the cyclization products **2c** and **5c** (Figure 2). But for the cyclization of model **6**, the 6-*endo* products (*trans*/*cis*-**8**) are more stable than 5-*exo* products (*trans*/*cis*-**7**) in both CH_2Cl_2 and a vacuum, and *cis*-**8** is more stable than *trans*-**8** due to the favorable diequatorial orientation of the two substituents on the cyclohexane skeleton. Therefore, we conclude that the *trans*-5-*exo* mode for the cyclization of **1a**−**d** to form lactams is both kinetically and thermodynamically preferred, whereas for the cyclization of compound **I** to form a carbocycle, the *cis*-6-*endo* product is preferred under thermodynamic control.

***N*-Allyl-Type Substrates 1f and 1g with a Double Bond as Part of the Carbocycle.** The structures of pyrrolidine or

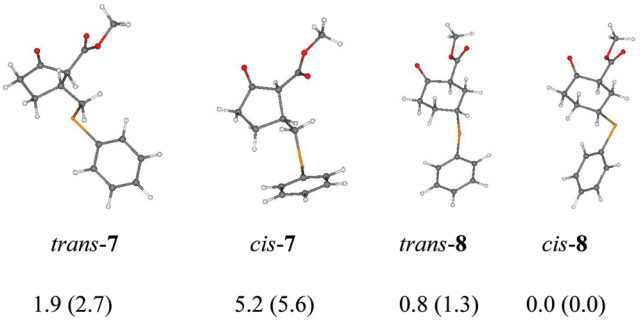

FIGURE 3. Calculated structures (*trans*/*cis*-**7** and *trans*/*cis*-**8**) and relative energies (kcal/mol) in CH_2Cl_2 and in vacuum (in parentheses).

piperidine ring fused to other rings in a variety of ways are core skeletons of many alkaloids and therapeutic agents. Bicyclic nitrogen heterocycles are important building blocks for their synthesis. Some key intermediates of the synthesis of (+)-coccinine,[27a] pancracine,[27b] and a PGD_2 receptor antagonist[27c] as well as the bicyclic nitrogen heterocycle nature product lepadin[27d] are shown in Figure 4.

To construct bicyclic nitrogen heterocycles, we prepared the *N*-allyl-type substrates **1f** and **1g**, with the double bond being part of the ring, as precursors for PhSe group transfer radical cyclization. By subjecting compounds **1f** and **1g** to the above cyclization conditions, bicyclic nitrogen heterocycles

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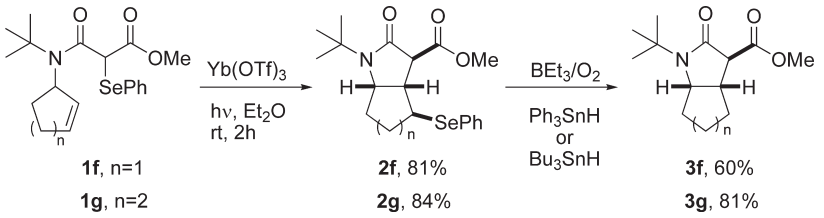
(27) (a) Pearson, W. H.; Lian, B. W. *Angew. Chem., Int. Ed.* **1998**, *37*, 1724. (b) Overman, L. E.; Shim, J. *J. Org. Chem.* **1993**, *58*, 4662. (c) Campos, K. R.; Journet, M.; Lee, S.; Grabowski, E. J. J.; Tillyer, R. D. *J. Org. Chem.* **2005**, *70*, 268. (d) Ozawa, T.; Aoyagi, S.; Kibayashi, C. *Org. Lett.* **2000**, *2*, 2955.

SCHEME 3. Construction of Bicyclic Nitrogen Heterocycles via PhSe Group Transfer Radical Cyclization of 1f and 1g



were obtained in high yields with excellent stereoselectivities (Scheme 3). Four stereocenters were established in one single step.

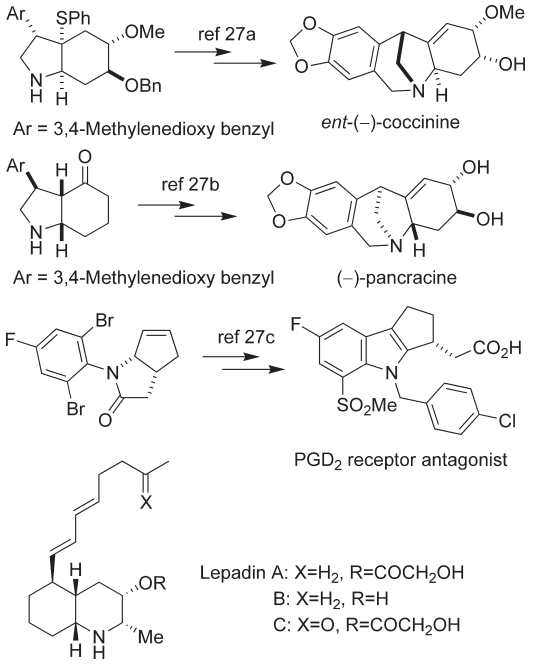


FIGURE 4. Examples of natural products and pharmaceutically relevant molecules.

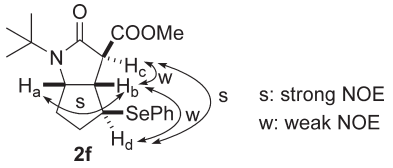
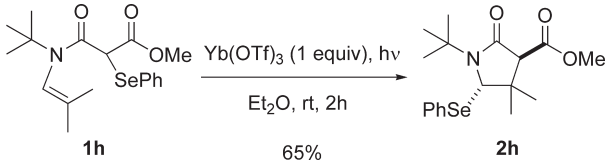


FIGURE 5. NOE correlations of compound **2f**.

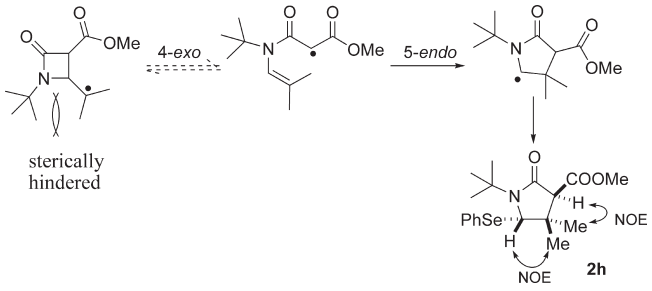
The stereochemistry of compound **2f** was determined by 2D-NOESY spectroscopy. Strong NOE was observed between two bridgehead protons H_a and H_b, as well as H_c and H_d, while weak NOEs are observed for the pairs of H_b/H_c and H_b/H_d (Figure 5). This NOE pattern indicates that the two five-membered rings are *cis*-fused.[15] The ester group is *syn* to the bridgehead protons and the PhSe group radical is captured from the convex face. The stereochemistry of product **2g** was confirmed by X-ray crystallographic analysis of **3g**,[15] the reductive dephenylselenation product of **2g**. Compound **3g** has a *cis*-fused bicyclic structure, and its ester group is *cis* to the bridgehead protons.

Enamide-Type Substrate 1h. The radical cyclization of enamides usually proceeds in 4-*exo* mode.[28] When the enamide substrate **1h** was subjected to the above PhSe group transfer radical cyclization conditions, a 3,5-*trans*-substituted 5-*endo* mode cyclization product **2h** was obtained exclusively in 65% yield (Scheme 4). 2D NMR analysis revealed that the ring closure of substrate **1h** proceeded via 5-*endo-trig* mode cyclization, and the 3-ester group was *trans* to the 5-PhSe group.

SCHEME 4. PhSe Group Transfer Radical Cyclization of Enamide 1h



SCHEME 5. Plausible Mechanism of PhSe Group Transfer Radical Cyclization of Enamide 1h



A plausible mechanism for the cyclization of **1h** is shown in Scheme 5. The 5-*endo-trig* mode of radical cyclization is generally considered a "disfavored" process according to the Baldwin−Beckwith rules.[19,21a] However, recently reported theoretical studies suggest that the 5-*endo-trig* mode of cyclization is strongly favored over the 4-*exo* cyclization not only thermodynamically but also kinetically in the absence of steric or conformational effects.[29] For the α-radical generated from substrate **1h**, the steric effect between *tert*-butyl group on the nitrogen atom and the isopropyl substituent would hinder the 4-*exo* cyclization (Scheme 5). Therefore, the 5-*endo* mode cyclization is preferred. Furthermore, the *trans* stereochemistry of the 3-ester

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(29) Chatgilialoglu, C.; Ferreri, C.; Guerra, M.; Timokhin, V.; Froudakis, G.; Gimisis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10765.

group and the 5-PhSe group is favored to avoid the steric clash between them.

Conclusion

In conclusion, Lewis acid-promoted PhSe group transfer radical cyclization represents an efficient, regiospecific, and stereoselective strategy for the formation of highly functionalized monocyclic and bicyclic nitrogen heterocyles, which constitute important core structures of many biologically interesting natural products and therapeutic agents. The method is highly flexible and encompasses a broad substrate scope. Given its mild reaction conditions and high yields and selectivities, this synthetic approach to lactams and ring-fused nitrogen heterocyles possesses clear intrinsic advantages. Future efforts will be steered toward developing methods for enantioselective radical cyclization.

Experimental Section

A 320 nm, 125W high-pressure mercury lamp was used as the UV source. The reactions were carried out in Pyrex glass flasks.

General Procedure for the Group Transfer Radical Cyclization. Methyl *trans*-1-*tert*-Butyl-2-oxo-4-(1-phenylselenoethyl)-pyrrolidine-3-carboxylate (2a). To a stirred solution of $Yb(OTf)_3$ (386 mg, 0.62 mmol) in Et_2O (10 mL) was added a solution of **1a** (238 mg, 0.62 mmol) in Et_2O (20 mL) at −78 °C. The system was deoxygenated with N_2 for 0.5 h at −78 °C and then irradiated with a UV lamp at room temperature. After 2 h, the reaction mixture was diluted with Et_2O and washed with water. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography to give **2a** (203 mg, 85%) as a light yellow oil. Analytical TLC (silica gel 60): 50% EtOAc in *n*-hexane, R_f = 0.51; ^{1}H NMR (400 MHz, $CDCl_3$) (diastereomer ratio 7/3) δ 7.57−7.54 (m, 2H), 7.34−7.27 (m, 3H), 3.79 (s, 0.3 × 3H), 3.74 (s, 0.7 × 3H), 3.69 (dd, J = 9.8, 8.5 Hz, 0.7 × 1H), 3.60 (dd, J = 10.4, 8.7 Hz, 0.3 × 1H), 3.39 (d, J = 8.2 Hz, 0.3 × 1H), 3.38 (d, J = 8.7 Hz, 0.7 × 1H), 3.29−3.14 (m, 2H), 2.97−2.84 (m, 1H), 1.41 (d, J = 6.7 Hz, 3H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 168.9, 135.3, 135.2, 129.2, 128.1, 128.0, 55.4, 55.2, 54.84, 54.80, 52.7, 52.6, 49.1, 47.7, 43.1, 42.3, 41.6, 40.8, 27.6, 20.4, 19.4; IR (neat) 2970, 1741, 1689 cm^{-1}; LRMS for $C_{18}H_{25}NO_3Se$ (EI, 20 eV) m/z 384 (M^+ + 1, 6), 383 (M^+, 51), 170 (88), 138 (100); HRMS (EI) for $C_{18}H_{25}NO_3Se$ (M^+) calcd 383.1000, found 383.1000.

Methyl 1-*tert*-butyl-2-oxo-4-(phenylselenomethyl)pyrrolidine-3-carboxylate (2b): yellow oil, 85% yield; analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, R_f = 0.33; ^{1}H NMR (400 MHz, $CDCl_3$) (diastereomer ratio 13.4/1) δ 7.52−7.50 (m, 2H), 7.30−7.26 (m, 3H), 3.76 (s, 0.93 × 3H), 3.72 (s, 0.07 × 3H), 3.66 (dd, J = 9.9, 7.6 Hz, 0.93 × 1H), 3.58 (dd, J = 9.2, 7.8 Hz, 0.07 × 1H), 3.41 (d, J = 8.7 Hz, 0.07 × 1H), 3.33 (t, J = 9.2 Hz, 0.07 × 1H), 3.27 (d, J = 8.0 Hz, 0.93 × 1H), 3.11 (dd, J = 9.9, 6.7 Hz, 0.93 × 1H), 3.07−3.02 (m, 1H), 2.95−2.87 (m, 2H), 1.37 (s, 0.07 × 9H), 1.36 (s, 0.93 × 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 168.8, 133.4, 133.2, 129.4, 129.2, 127.7, 127.6, 56.6, 54.9, 54.8, 52.7, 52.3, 50.7, 49.8, 36.1, 35.9, 31.0, 27.6; IR (neat) 2972, 1740, 1689, 740, 692 cm^{-1}; LRMS for $C_{17}H_{23}NO_3Se$ (EI, 20 eV) m/z 369 (M^+, 100), 212 (95); HRMS (EI) for $C_{17}H_{23}NO_3Se$ (M^+) calcd 369.0843, found 369.0855.

Methyl 1-*tert*-butyl-4-methyl-2-oxo-4-(phenylselenomethyl)-pyrrolidine-3-carboxylate (2c): yellow oil, 95% yield; analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, R_f = 0.51; ^{1}H NMR (400 MHz, $CDCl_3$) (diastereomer ratio 2.2:1) δ 7.55−7.50 (m, 2H), 7.29−7.25 (m, 3H), 3.71 (s, 0.7 × 3H), 3.68 (s, 0.3 × 3H), 3.50 (d, J = 9.6 Hz, 0.3 × 1H), 3.41 (d, J = 10.1 Hz, 0.7 × 1H), 3.28 (d, J = 9.6 Hz, 0.7 × 1H), 3.25 (s, 0.7 × 1H), 3.15−3.08 (m, 0.3 × 1H + 2H), 3.03 (d, J = 12.4 Hz, 0.3 × 1H), 1.34 (s, 0.3 × 9H), 1.28 (s, 0.3 × 3H and 0.7 × 9H), 1.13 (s, 0.7 × 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 169.5, 169.4, 169.3, 133.2, 133.1, 130.6, 130.5, 129.4, 129.3, 127.5, 127.4, 61.9, 60.9, 56.3, 55.2, 54.5(2), 52.3, 52.1, 40.7, 40.4, 35.6, 27.5(2), 26.2, 21.0; IR (neat) 2970, 1737, 1691 cm^{-1}; LRMS for $C_{18}H_{25}NO_3Se$ (EI, 20 eV) m/z 383 (M^+, 98), 226 (100), 212 (28); HRMS (EI) for $C_{18}H_{25}NO_3Se$ (M^+) calcd 383.1000, found 383.1006.

Methyl *trans*-1-*tert*-butyl-2-oxo-4-(2-(phenylseleno)propan-2-yl)pyrrolidine-3-carboxylate (2d): yellow oil, 95% yield; analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, R_f = 0.53; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 6.8 Hz, 2H), 7.41−7.29 (m, 3H), 3.76 (s, 3H), 3.60 (t, J = 9.3 Hz, 1H), 3.57 (d, J = 8.3 Hz, 1H), 3.39 (dd, J = 9.8, 7.3 Hz, 1H), 2.88−2.82 (m, 1H), 1.40 (s, 9H), 1.35 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 169.0, 138.4, 129.1, 129.0, 126.5, 54.9, 53.5, 52.7, 48.4, 47.0, 45.7, 28.4, 27.7, 27.0; IR (neat) 2963, 1741, 1689 cm^{-1}; LRMS for $C_{19}H_{27}NO_3Se$ (EI, 20 eV) m/z 397 (M^+, 7), 240 (75), 184 (100); HRMS (EI) for $C_{19}H_{27}NO_3Se$ (M^+) calcd 397.1156, found 397.1172.

Methyl *trans*-1-*tert*-butyl-2-oxo-4-(phenylselenomethyl)piperidine-3-carboxylate (2e): yellow oil, 83% yield; analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, R_f = 0.44; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.46 (m, 2H), 7.29−7.25 (m, 3H), 3.71 (s, 3H), 3.42 (dt, J = 11.9, 4.7 Hz, 1H), 3.27 (d, J = 10.6 Hz, 1H), 3.27−3.21 (m, 1H), 3.05 (dd, J = 12.8, 4.1 Hz, 1H), 2.69 (dd, J = 12.7, 8.3 Hz, 1H), 2.43−2.34 (m, 1H), 2.16 (dq, J = 13.4, 4.2 Hz, 1H), 1.54−1.46 (m, 1H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 166.4, 132.6, 130.1, 129.3, 127.2, 58.0, 57.7, 52.4, 42.9, 36.4, 32.5, 28.4, 28.2; IR (neat) 2955, 1740, 1644 cm^{-1}; LRMS for $C_{18}H_{25}NO_3Se$ (EI, 20 eV) m/z 384 (M^+ + 1, 9), 383 (M^+, 46), 226 (64), 170 (100); HRMS (EI) for $C_{18}H_{25}NO_3Se$ (M^+) calcd 383.1000, found 383.0992.

Methyl *cis*-1-*tert*-butyl-2-oxo-*cis*-4-(phenylseleno)octahydrocyclopenta[*b*]pyrrole-*cis*-3-carboxylate (2f): yellow oil, 81% yield; analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, R_f = 0.33; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−7.51 (m, 2H), 7.31−7.26 (m, 3H), 4.33 (td, J = 8.0, 5.0 Hz, 1H), 3.69 (s, 3H), 3.50−3.46 (m, 1H), 3.20 (d, J = 6.9 Hz, 1H), 3.03 (ddd, J = 8.0, 6.9, 4.1 Hz, 1H), 2.31−2.15 (m, 2H), 1.79−1.65 (m, 2H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 168.4, 134.8, 129.3, 128.6, 128.0, 61.6, 55.9, 55.2, 52.7, 47.2, 46.3, 34.4, 32.0, 28.2; IR (neat) 2961, 1740, 1685, 1578 cm^{-1}; LRMS for $C_{19}H_{25}NO_3Se$ (EI, 20 eV) m/z 395 (M^+, 58), 150 (100); HRMS (EI) for $C_{19}H_{25}NO_3Se$ (M^+) calcd 395.1000, found 395.0999.

Methyl *cis*-1-*tert*-butyl-2-oxo-*cis*-4-(phenylseleno)octahydro-1*H*-indole-*cis*-3-carboxylate (2g): yellow oil, 84% yield; analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, R_f = 0.29; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−7.51 (m, 2H), 7.31−7.27 (m, 3H), 3.95 (dt, J = 11.5, 6.0 Hz, 1H), 3.72−3.67 (m, 4H), 3.43 (d, J = 12.8 Hz, 1H), 2.99 (dd, J = 12.8, 6.4 Hz, 1H), 2.20−2.16 (m, 1H), 1.91−1.86 (m, 1H), 1.83−1.75 (m, 1H), 1.72−1.57 (m, 2H), 1.41 (s, 9H), 1.24−1.14 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 168.5, 133.9, 129.6, 129.3, 127.7, 54.9, 53.8, 52.7, 52.6, 42.9, 41.6, 31.6, 28.3, 26.1, 19.5; IR (neat) 2974, 1744, 1675 cm^{-1}; LRMS for $C_{20}H_{27}NO_3Se$ (EI, 20 eV) m/z 410 (M^+ + 1, 6), 409 (M^+, 36), 252 (27), 164 (100), 157 (6); HRMS (EI) for $C_{20}H_{27}NO_3Se$ (M^+) calcd 409.1156, found 409.1157.

Methyl *trans*-1-*tert*-butyl-4,4-dimethyl-2-oxo-5-(phenylseleno)-pyrrolidine-3-carboxylate (2h): yellow oil, 65% yield; analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, R_f = 0.57; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57−7.54 (m, 2H), 7.31−7.29 (m, 3H), 4.86 (s, 1H), 3.74 (s, 3H), 3.50 (s, 1H), 1.58 (s, 9H), 1.27 (s, 3H), 1.20 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 168.5, 134.4, 129.8, 129.6, 128.0, 76.4, 57.8, 55.9, 52.1, 44.5, 27.6, 25.2, 24.1; IR (neat) 2971, 1753, 1701 cm^{-1}; LRMS for $C_{18}H_{25}NO_3Se$ (EI, 20 eV) m/z 226 ($C_{12}H_{20}NO_3$, M^+ − SePh, 58), 170 (100); HRMS (EI) for

$C_{18}H_{25}NO_3Se$ calcd 226.1443 ($C_{12}H_{20}NO_3$, $M^+ - SePh$), found 226.1446.

General Procedure for the Oxidative Elimination of the Phenylseleno Group. Methyl *trans*-1-*t*ert-Butyl-2-oxo-4-vinylpyrrolidine-3-carboxylate (3a). H_2O_2 (0.12 mL, 1.06 mmol, 30 wt % in H_2O) was added to a solution of **2a** (223 mg, 0.58 mmol) in THF (25 mL) at 0 °C. The solution was then stirred overnight at room temperature. After removal of the solvent, the mixture was diluted with CH_2Cl_2 (30 mL), washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated. The crude residue was purified by flash column chromatography to provide **3a** (121 mg, 92%) as colorless oil: analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, R_f = 0.52; ^{1}H NMR (400 MHz, $CDCl_3$) (diastereomer ratio 9:1) δ 5.76 (ddd, J = 17.1, 10.3, 6.8 Hz, 1H), 5.18 (d, J = 17.1 Hz, 1H), 5.12 (d, J = 10.3 Hz, 1H), 3.78 (s, 0.9 × 3H), 3.70 (s, 0.1 × 3H), 3.66 (dd, J = 9.5, 7.6 Hz, 0.9 × 1H), 3.53 (d, J = 8.8 Hz, 0.1 × 2H), 3.42 (d, J = 8.8 Hz, 0.1 × 1H), 3.31−3.27 (m, 0.9 × 2H), 3.18−3.12 (m, 1H), 1.42 (s, 0.1 × 9H), 1.40 (s, 0.89 × 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 169.1, 136.4, 134.0, 118.6, 117.3, 55.8, 55.4, 54.7, 54.6, 52.6, 52.0, 49.6, 49.1, 40.1, 39.7, 27.6; IR (neat) 2975, 1743, 1691 cm^{-1}; LRMS for $C_{12}H_{19}NO_3$ (EI, 20 eV) m/z 226 (M^+ + 1, 6), 225 (M^+, 44), 210 (100); HRMS (EI) for $C_{12}H_{19}NO_3$ (M^+) calcd 225.1365, found 225.1364.

Methyl *trans*-1-*tert*-butyl-2-oxo-4-(prop-1-en-2-yl)pyrrolidine-3-carboxylate (3d): yellow oil, 92% yield; analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, R_f = 0.51; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.85 (s, 1H), 4.82 (s, 1H), 3.79 (s, 3H), 3.67 (t, J = 8.8 Hz, 1H), 3.40 (d, J = 9.6 Hz, 1H), 3.29 (q, J = 8.8 Hz, 1H), 3.20 (t, J = 8.8 Hz, 1H), 1.74 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 169.3, 142.8, 112.2, 54.8, 54.6, 52.6, 48.4, 42.5, 27.7, 20.4; IR (neat) 2972, 1743, 1691 cm^{-1}; LRMS for $C_{13}H_{21}NO_3$ (EI, 20 eV) m/z 241 (M^+ + 2, 51), 226 (100), 198 (48); HRMS (EI) for $C_{13}H_{21}NO_3$ (M^+) calcd 239.1521, found 239.1522.

General Procedure for the Reductive Dephenylselenation. Methyl *trans*-1-*t*ert-Butyl-4-methyl-2- oxopyrrolidine-3-carboxylate (3b). To a stirred solution of **2b** (111 mg, 0.30 mmol) in dry benzene (10 mL) was added Bu_3SnH (0.16 mL, 0.60 mmol) at room temperature. Et_3B (1 M *n*-hexane solution, 0.29 mL, 0.29 mmol) and oxygen gas (7 mL) were added via syringe. The reaction was complete 3.5 h later. After removal of benzene, the residue was diluted with Et_2O. DBU (48 μL, 0.32 mmol) was added followed by I_2/Et_2O solution until the light yellow color persisted. The precipitate was filtered off, and the filtrate was concentrated. The crude product was purified by column chromatography to give **3b** (53 mg, 82%) as a white solid: mp 65−66 °C; analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, R_f = 0.30; ^{1}H NMR (400 MHz, $CDCl_3$) (diastereomer ratio 95/5) δ 3.78 (s, 0.95 × 3H), 3.72 (s, 0.05 × 3H), 3.65 (dd, J = 9.3, 7.8 Hz, 0.95 × 1H), 3.52 (dd, J = 9.3, 7.3 Hz, 0.05 × 1H), 3.34 (d, J = 9.3 Hz, 0.05 × 1H), 3.23 (t, J = 9.1 Hz, 0.05 × 1H), 3.03 (d, J = 8.3 Hz, 0.95 × 1H), 2.97 (dd, J = 9.3, 7.8 Hz, 0.95 × 1H), 2.74−2.63 (m, 1H), 1.41 (s, 0.05 × 9H), 1.39 (s, 0.95 × 9H), 1.13 (d, J = 6.8 Hz, 0.95 × 3H), 1.05 (d, J = 6.8 Hz, 0.05 × 3H); ^{13}C NMR (100 MHz, $CDCl_3$) (major diastereomer) δ 170.6, 169.7, 58.1, 54.5, 52.5, 51.4, 30.9, 27.7, 18.3; IR (neat) 2926, 1742, 1690 cm^{-1}; LRMS for $C_{11}H_{19}NO_3$ (EI, 20 eV) m/z 213 (M^+, 62), 198 (100); HRMS (EI) for $C_{11}H_{19}NO_3$ (M^+) calcd 213.1365, found 213.1371.

Methyl 1-*t*ert-butyl-4,4-dimethyl-2-oxopyrrolidine-3-carboxylate (3c): yellow oil, 87% yield; analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, R_f = 0.45; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 3H), 3.38 (d, J = 9.3 Hz, 1H), 3.11 (d, J = 9.3 Hz, 1H), 2.99 (s, 1H), 1.41 (s, 9H), 1.21 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 169.8, 62.1, 57.9, 54.2, 51.9, 35.7, 28.7, 27.6, 22.6; IR (neat) 2964, 1739, 1690 cm^{-1}; LRMS for $C_{12}H_{21}NO_3$ (EI, 20 eV) m/z 227 (M^+, 57), 212 (100), 170 (3); HRMS (EI) for $C_{12}H_{21}NO_3$ (M^+) calcd 227.1521, found 227.1530.

Methyl *trans*-1-*tert*-butyl-4-methyl-2-oxopiperidine-3-carboxylate (3e): yellow oil, 81% yield; analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, R_f = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (s, 3H), 3.45−3.38 (m, 1H), 3.26 (td, J = 11.6, 4.4 Hz, 1H), 2.98 (d, J = 11.0 Hz, 1H), 2.21−2.15 (m, 1H), 1.89 (dq, J = 13.7, 3.9 Hz, 1H), 1.46−1.35 (m, 10H), 0.97 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 167.0, 59.6, 57.8, 52.2, 43.2, 31.0, 30.8, 28.1, 20.1; IR (neat) 2958, 1743, 1643 cm^{-1}; LRMS for $C_{12}H_{21}NO_3$ (EI, 20 eV) m/z 228 (M^+ + 1, 15), 227 (M^+, 100), 212 (87); HRMS (EI) for $C_{12}H_{21}NO_3$ (M^+) calcd 227.1521, found 227.1549.

Methyl *cis*-1-*tert*-butyl-2-oxooctahydrocyclopenta[*b*]pyrrole-*cis*-3-carboxylate (3f): yellow oil, 60% yield; analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, R_f = 0.33; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (td, J = 7.8, 4.1 Hz, 1H), 3.77 (s, 3H), 3.19 (d, J = 6.9 Hz, 1H), 3.03 (qd, J = 7.8, 3.6 Hz, 1H), 1.92−1.50 (m, 6H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 169.3, 62.4, 56.7, 54.9, 52.6, 40.0, 35.3, 31.9, 28.2, 24.6; IR (neat) 2960, 1741, 1683 cm^{-1}; LRMS for $C_{13}H_{21}NO_3$ (EI, 20 eV) m/z 239 (M^+, 48), 224 (100); HRMS (EI) for $C_{13}H_{21}NO_3$ (M^+) calcd 239.1521, found 239.1524.

Methyl *cis*-1-*tert*-butyl-2-oxo-octahydro-*1H*-indole-*cis*-3-carboxylate (3g): yellow oil, 81% yield; analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, R_f = 0.44; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 3.65−3.59 (m, 1H), 3.46 (d, J = 13.3 Hz, 1H), 2.82−2.76 (m, 1H), 2.14−2.10 (m, 1H), 1.76−1.72 (m, 2H), 1.60−1.56 (m, 2H), 1.41 (s, 9H), 1.30−1.11 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 169.6, 56.4, 54.6, 52.5, 51.6, 37.3, 31.8, 28.3, 25.4, 23.2, 20.4; IR (neat) 2945, 1740, 1688 cm^{-1}; LRMS for $C_{14}H_{23}NO_3$ (EI, 20 eV) m/z 254 (M^+ + 1, 9), 253 (M^+, 63), 238 (100), 196 (7); HRMS (EI) for $C_{14}H_{23}NO_3$ (M^+) calcd 253.1678, found 253.1681.

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Supporting Information Available: Synthetic schemes and characterization data of compounds **1a**−**h**, NMR spectra of compounds **1a**−**h**, **2a**−**h**, **3a**−**g**, and **4a**−**h**, and crystallographic data of compound **3g**. Theoretical calculation details of **2b/c**, **5b/c**, **7**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.