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Development of efficient new methodology for generation, cyclization and functional trapping of iminyl and amidyl radicals

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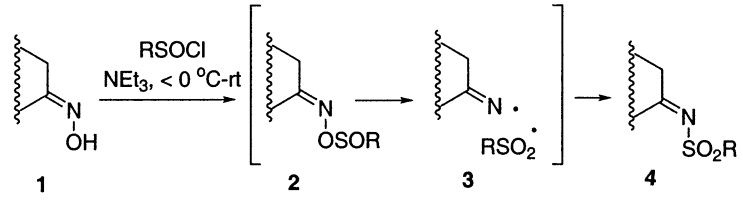
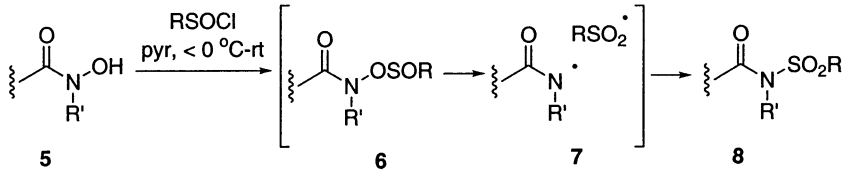
Abstract—New methodology has been devised for the generation and subsequent cyclization of iminyl and amidyl radicals under mild conditions. The process involves either the treatment of oximes with 2,6-dimethylbenzenesulfinyl chloride, or the treatment of hydroxamic acids with *tert*-butylsulfinyl chloride (−50°C to rt), to give the corresponding nitrogen radicals, followed by cyclization onto pendant olefins. Radical traps such as diphenyl diselenide, diphenyl disulfide, and TEMPO can be used to terminate the cyclizations, thus introducing functionality that provides multiple options for further manipulation. In a more convenient procedure, both iminyl and amidyl radical cyclizations can be initiated using commercially available diethyl chlorophosphite which generally provides similar (with diphenyl disulfide and TEMPO) or significantly higher (with diphenyl diselenide) yields of products.

1. Introduction and background

An attractive strategy for constructing nitrogen heterocycles involves the cyclization of a nitrogen-centered radical onto a pendant olefin.[1] During the past decade a considerable amount of methodology has been developed to effect this type of transformation in a synthetically useful manner, with aminyl, iminyl[2] and amidyl[3] radicals receiving significant attention. In particular, the innovative studies of Newcomb and of Zard have led to a variety of clever methods for generating different types of nitrogen radicals, and also to a better understanding of the reactivity of these species. However, this field has not received nearly the attention as have carbon-centered radicals. As part of our long-standing research on the total synthesis of alkaloids and other nitrogen-containing natural products, we became interested in the prospect of utilizing nitrogen radical cyclizations to efficiently access highly functionalized intermediates. A major goal of our research was to develop flexible, operationally simple new methodology to effect nitrogen radical–olefin cyclizations which would also allow trapping of the resulting carbon radical with a variety



Scheme 1.



Scheme 2.

Keywords: iminyl radicals; amidyl radicals; cyclization.

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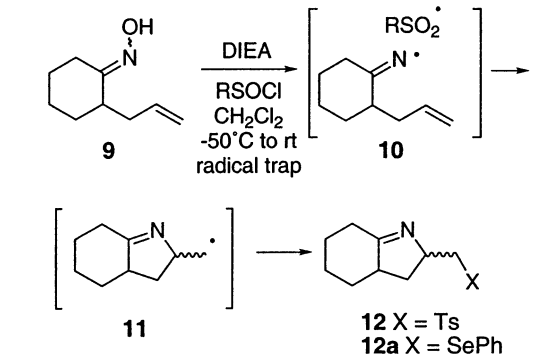


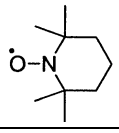
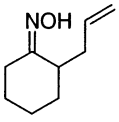
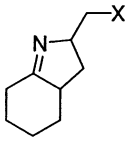
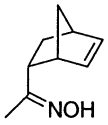
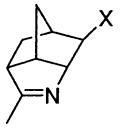
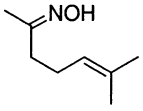
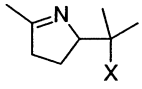
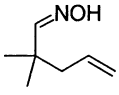
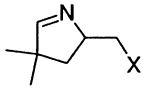
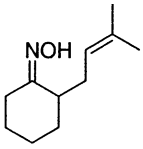
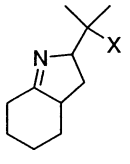
R = *p*-tol	**12** (19%)
R = *p*-tol/Ph_2Se_2	**12a** (22%)
R = Bn/Ph_2Se_2	(41%)
R = cinnamyl/Ph_2Se_2	(27%)
R = *tert*-Bu/Ph_2Se_2	(47%)
R = 2,6-dimethylphenyl/Ph_2Se_2	(61%)
R = 2,4,6-triisopropylphenyl/Ph_2Se_2	(23%)

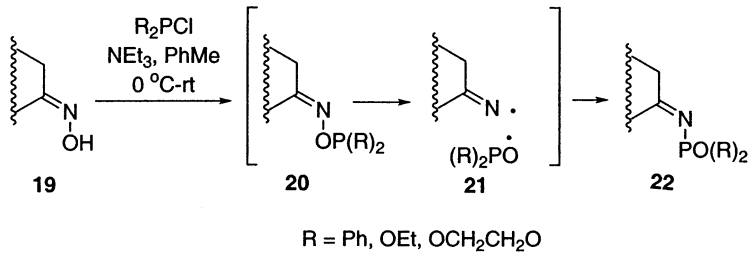
Scheme 3.

of heteroatoms (rather than a hydrogen), thereby leading to products readily amenable to subsequent functional group manipulations.[4]

Towards this goal, we were attracted by the report of Hudson and coworkers that treatment of an oxime **1** with a sulfinyl chloride at low temperature, followed by warming to room temperature, leads to an *N*-sulfonylimine **4** (Scheme 1).[5,6] In a series of mechanistic experiments based on NMR and EPR spectroscopy, it was convincingly shown that this process involves initial formation of sulfinate ester **2** which upon warming undergoes spontaneous homolysis to an iminyl/sulfonyl 'caged' radical pair **3**. Subsequent recombination of this radical pair then affords the observed product **4**. A closely related reaction is also known for various hydroxamic acid derivatives.[7] Thus, a hydroxamic acid **5** reacts with a sulfinyl chloride to ultimately produce an *N*-sulfonylamide **8** (Scheme 2). Once again, mechanistic evidence indicated that this transformation occurs via sulfinate **6** and amidyl/sulfonyl radical pair **7**. It was also shown by isotopic labelling experiments that radical pair

Table 1. Isolated yields of radical cyclization products of oxime olefins

Oxime[13]	Product	Radical traps					
		PhSeSePh		PhSSPh			
		X=SePh		X=SPh		X=TEMPO	
		ArSOCl	$(EtO)_2PCl$	ArSOCl	$(EtO)_2PCl$	ArSOCl	$(EtO)_2PCl$
 **9**		61% **12a**	86%	70% **12b**	69%	61% **12c**	41%
 **13**		58% **13a**	86%	67% **13b**	68%	58% **13c**	64%
 **14**		49% **14a**	72%	60% **14b**	61%	49% **14c**	58%
 **15**		49% **15a**		56% **15b**			
 **16**		65% **16a**		75% **16b**		62% **16c**	



Scheme 4.

recombination is intramolecular.[7d] However, despite the apparent simplicity and mildness of generating iminyl and amidyl radicals by these processes, to our knowledge no attempt had ever been made to intercept these radicals with an internal alkene. In this paper we describe the full details of our exploratory work in this area.[4]

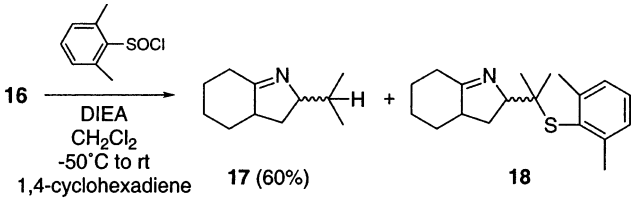
2. Results and discussion

2.1. Iminyl radical cyclizations

Preliminary feasibility experiments were conducted with oxime **9** derived from commercially available 2-allylcyclohexanone. The hope was that the initially formed iminyl radical (cf. **10**) would cyclize more rapidly than recombination to the *N*-sulfonylimine, and that the resulting carbon centered radical **11** would then react with a sulfonyl radical to afford **12** (X=Ts) (Scheme 3).[8] In fact, treatment of oxime **9** with *p*-toluenesulfinyl chloride[9] did give bicyclic imine sulfone **12**, but only in low yield with the major by-product in this reaction being the uncyclized *N*-sulfonylimine. The cyclization could not be improved significantly by adding diphenyl diselenide as a radical trap, and only a poor 22% yield of imine selenide **12a** was obtained, with the *N*-sulfonylimine once again being the major product.

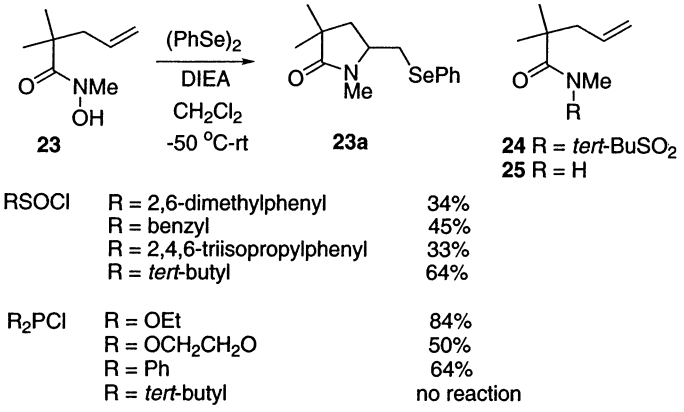
It therefore became evident that in order to make this approach viable it was necessary to interfere with or slow the radical recombination step, and we considered two sulfinyl chloride-based strategies. The first was to generate a sulfonyl radical which should be prone to rapid loss of SO_2 by producing a stabilized alkyl radical, thereby preventing *N*-sulfonylimine formation.[9,10] The other was to use bulky sulfinyl chlorides and slow radical recombination by steric factors. Thus, treatment of oxime olefin **9** with benzylsulfinyl chloride/diphenyl diselenide indeed led to a substantial improvement in the yield of cyclization product **12a** to 41%. In support of the premise that loss of sulfur dioxide from the benzylsulfonyl radical was atleast partially occurring was the fact that we isolated benzyl phenyl selenide in 24% yield. It might also be noted that use of Hunig's base provided slightly better yields of product **12a** than did triethylamine, and was superior to DMAP, NaH, *tert*-BuOK, pyridine or 2,6-di-*tert*-butylpyridine in exploratory reactions using benzylsulfinyl chloride. In addition, methylene chloride was a far better solvent than THF, toluene, acetonitrile, ether or chlorobenzene. Although cinnamylsulfinyl chloride did not prove useful, *tert*-butylsulfinyl chloride,[11] which in principle can work via both of the effects mentioned above, did lead to an improved 47% yield of selenide **12a**. This reaction also produced about 14% of *tert*-butyl phenyl selenide. The best reagent, however, proved to be bulky 2,6-dimethylbenzenesulfinyl chloride[12] which provided **12a** in 61% isolated yield. The product yield was reduced, however, when the even more sterically hindered compound 2,4,6-triisopropylbenzenesulfinyl chloride was used, perhaps due to difficulties in the initial oxime sulfinylation step.

Using the optimum experimental conditions found for **12a**, a series of oxime olefin substrates[13] was examined and the results are shown in Table 1. The reactions are best performed by treating the oxime in methylene chloride with 2,6-dimethylbenzenesulfinyl chloride (2 equiv.) initially at −50°C in the presence of Hunig's base and a radical trapping agent, and then slowly warming the mixture to room temperature. With diphenyl diselenide or TEMPO as the trapping agents, only a small excess was required to provide the desired products in acceptable isolated yields. However, with less reactive trapping reagents[14,15] such as diphenyl disulfide or 1,4-cyclohexadiene, a large excess must be used or significant amounts of side products are produced. For example, exposure of oxime **16** to the standard cyclization conditions in the presence of 100 equiv. of 1,4-cyclohexadiene as a hydrogen atom source afforded the desired reduced product **17** in moderate yield (Eq. (1)), but if substantially smaller quantities of this trap were used varying amounts of the sulfur-containing by-product **18** were formed.[16]



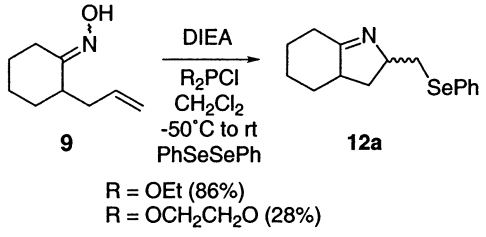
(1)

More recently we have investigated modifications of this methodology with the intent of increasing the yields of cyclization products and also finding an alternative, commercially available initiating reagent. One possible solution which occurred to us was to make use of a related reaction of oximes **19** with trivalent phosphorus compounds known to produce *N*-phosphinylimines **22** (Scheme 4).[17,18] This transformation, as in the case of the corresponding sulfinyl reaction in Scheme 1, has been shown in mechanistic studies by Hudson and coworkers to proceed via a radical pair **21** formed by homolytic dissociation of the initial intermediate **20**.[17b,c] An analogous reaction has also been described for the conversion of hydroxamic acids to *N*-phosphinylamides (cf. Scheme 2, vide infra).[19]



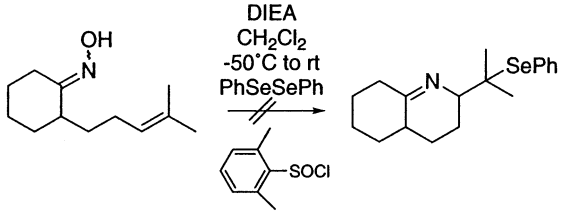
Scheme 5.

Exploratory reactions were conducted using oxime olefin **9** as the substrate and diphenyl diselenide as the radical trap (Eq. (2)). Some commercially available phosphorus reagents were tried, and we were pleased to find that diethyl chlorophosphite afforded a yield of product **12a** which was significantly better than that obtained with the sulfinyl reagent. Using diphenylchlorophosphine only led to the uncyclized *N*-phosphinylimine. In addition, diisopropylethylamine was still the most effective base. Table 1 contains the results of several cyclizations using these newly developed conditions. In general, cyclizations with diphenyl diselenide (2 equiv.) as the trap proceeded in superior yields compared to those done with 2,6-dimethylbenzenesulfinyl chloride. The reactions with diphenyl disulfide (10–20 equiv.) and TEMPO (2 equiv.) could be effected in yields comparable to those using the sulfinyl reagent.



(2)

An attempt was also made to effect a 6-*exo* iminyl radical cyclization to produce a six-membered ring imine (Eq. (3)). However, none of the desired product was formed. It is known that 6-*exo* iminyl radical cyclizations are about two orders of magnitude slower than the corresponding 5-*exo*closures, and thus radical recombination and other side processes evidently become favored in this system.[15] It might also be noted that there are few existing examples of 6-*exo* cyclizations of nitrogen radicals.[1–3]



(3)

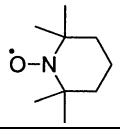
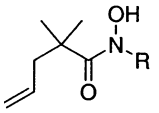
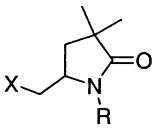
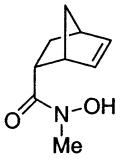
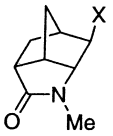
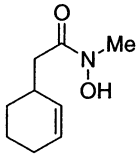
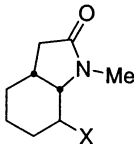
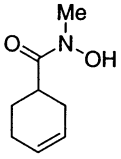
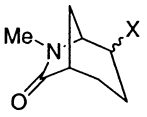
2.2. Amidyl radical cyclizations

In view of the successful results described above for the iminyl radical cyclizations, we next turned to an exploration of the feasibilty of effecting amidyl radical cyclizations via the same strategy. Hydroxamic acid olefin **23** was selected as the test substrate, and diphenyl diselenide as the radical trapping agent (Scheme 5). Initial experiments were conducted with various sulfinyl chlorides as the activating reagent, and isolated yields of cyclization product **23a** are shown in Scheme 5. Inexplicably, 2,6-dimethylbenzenesulfinyl chloride, which is most effective in the iminyl radical cases, did not work well in the amidyl system. Of all the sulfinyl compounds tried, *tert*-butylsulfinyl chloride (1.5 equiv.) in fact proved best, with cyclization product **23a** isolated in 64% yield. In addition, the radical recombination product **24** was formed in 14% yield along with 6% of reduced amide **25**, and 10% of the starting hydroxamic acid **23**.

Using the experimental conditions optimized for substrate **23**, a series of cyclizations was investigated on the olefinic hydroxamic acids listed in Table 2. Once again, diphenyl diselenide, diphenyl disulfide and TEMPO all proved to be effective radical trapping agents. As with the iminyl radical reactions, PhSSPh must be used in large excess.[20] After discovering that phosphorus reagents could be efficiently employed in initiating the iminyl radical cyclizations (vide supra), we returned to the hydroxamic acid substrate **23** to study this modification in the amidyl radical series. Indeed, diethyl chlorophosphite (1.5 equiv.) again proved to be very effective in initiating the reaction and the yield of selenide **23a** was substantially improved over that obtained with *tert*-butylsulfinyl chloride (Scheme 5). Some additional examples of cyclizations with this reagent are shown in Table 2. As can be seen, yields of selenide cyclization products are signifcantly improved and those using the other radical traps are similar to the sulfinyl chloride results. It might also be noted that we have been unable to effect a 6-*exo* cyclization in the amidyl series.

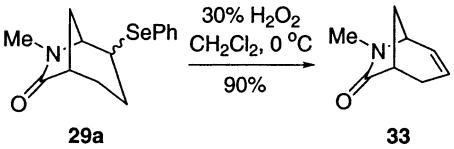
The feasibility of using the methodology in a tandem cyclization was also tested as shown in Scheme 6.[21] Thus, exposure of hydroxamic acid diene **30** to *tert*-butylsulfinyl chloride and PhSeSePh under our standard conditions led to bicyclic lactam selenide **32** (59%, 2:1 mixture of

Table 2. Isolated yields of radical cyclization products of olefinic hydroxamic acids

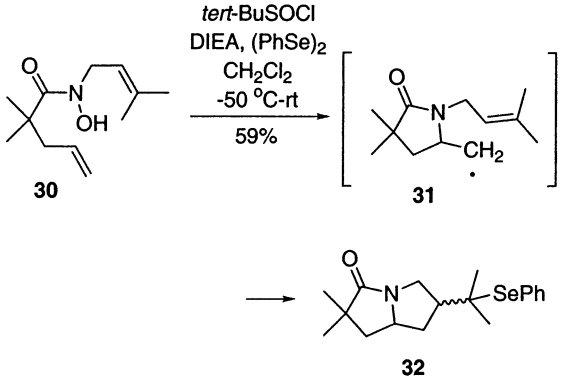
Hydroxamic Acid	Product	Radical traps					
		PhSeSePh		PhSSPh			
		X=SePh		X=SPh		X=TEMPO	
		tert-BuSOCl	$(EtO)_2PCl$	*tert*-BuSOCl	$(EtO)_2PCl$	*tert*-BuSOCl	$(EtO)_2PCl$
 **23** (R = Me) **26** (R = Bn)		64% **23a** 70% **26a**	84%	58% **23b** 74% **26b**	58%	60% **23c** 78% **26c**	67%
 **27**		65% **27a**	83%	64% **27b**	63%	62% **27c**	59%
 **28**		59% **28a**		56% **28b**		56% **28c**	
 **29**		58% **29a**	79%	61% **29b**	75%	57% **29c**	61%

diastereomers) via the intermediate monocyclic carbon-centered radical **31**. This cyclization was also effected with diethyl chlorophosphite but a by-product, $(EtO)_2P(O)$-SePh, could not be separated chromatographically from the desired compound **32**.

Prior to applying this cyclization methodology to an alkaloid synthesis (vide infra), we examined a further transformation of the bicyclic selenide product **29a**. As hoped, treatment of this material with hydrogen peroxide cleanly led to the desired bicyclic olefin **33** (Eq. (4)).[22]



29a **33** (4)

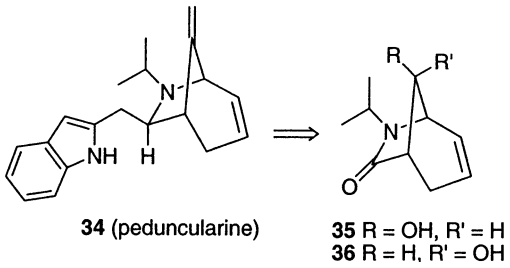


30 **31** **32**

Scheme 6.

2.3. Formal total synthesis of (+/−)-peduncularine via an amidyl radical cyclization

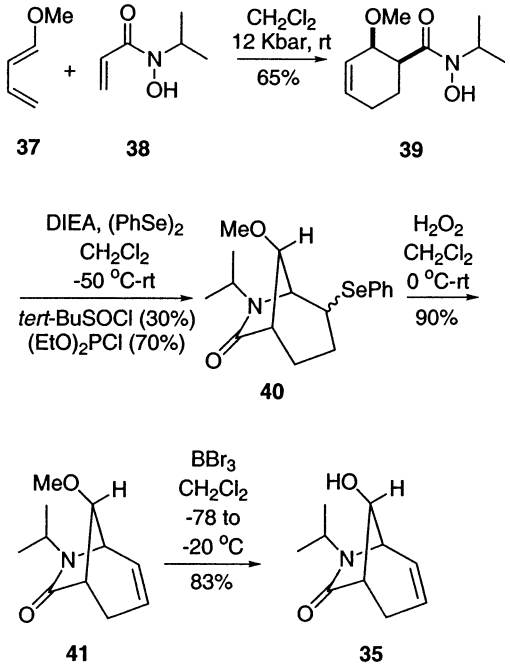
The indole alkaloid peduncularine (**34**) is a major metabolite of the Tasmanian shrub *Aristotelia peduncularis*.[23] This compound has an unusual 6-azabicyclo[3.2.1]-3-octene skeleton not previously found in indole alkaloids. Plants of the *Aristotelia* genus have long been used in folk medicine in New Zealand and South America, and peduncularine itself shows weak antitumor activity. Three total syntheses of peduncularine have emanated from the



Scheme 7.

groups of Hiemstra,[24a] Rigby[24b] and Woerpel.[24c] The Hiemstra synthesis, which was also enantioselective, involved elaboration of the key bicyclic alcohol lactam **35**, whereas both the Rigby and Woerpel racemic approaches proceeded via the epimeric alcohol **36** (Scheme 7).

It occurred to us that the amidyl radical cyclization methodology described above might provide a short, direct and efficient route to the pivotal Hiemstra peduncularine intermediate **35**. Our approach began with hydroxamic acid **38** which was easily prepared from acryloyl chloride and commercially available *N*-isopropylhydroxylamine hydrochloride (Scheme 8). Attempted Diels–Alder reaction of this compound with 1-methoxybutadiene (**37**) by heating in toluene, or using various Lewis acid catalysts led to complex mixtures of products. However, the cycloaddition proceeded smoothly at 12 Kbar at room temperature to afford the desired adduct **39** as a single stereoisomer. Exposure of this hydroxamic acid to *tert*-butylsulfinyl chloride/PhSeSePh under the usual conditions provided the requisite cyclization product **40** but only in a modest 30% yield. However, we were pleased to find that using diethyl chlorophosphite led to a dramatic increase in the yield of bicyclic selenide **40** to 70%. Compound **40** is a single isomer whose stereostructure has not been established.



Scheme 8.

Lactam selenide **40** was then oxidized with hydrogen peroxide as was done in the model system **29a** to afford the desired bicyclic alkene **41** in high yield.[22] Finally, the methyl ether group of **41** could be cleaved with BBr_3 to give the alcohol **35**. This compound had NMR spectra identical to those of an authentic sample.[25] Thus, alcohol **35** can be synthesized in only four steps in good overall yield from acrylate hydroxamic acid **38**. Since Hiemstra and coworkers[24a] have previously converted bicyclic lactam **35** to peduncularine (**34**), our synthesis of this intermediate constitutes a formal racemic total synthesis of this interesting alkaloid.

3. Conclusion

In this paper we have reported efficient, experimentally simple new methodology for effecting iminyl and amidyl radical/olefin cyclizations starting from readily available oximes and hydroxamic acids, respectively. The cyclizations can be terminated with various radical traps such as diphenyl diselenide, diphenyl disulfide and TEMPO, thereby providing products which are more highly functionalized than those produced by related tin hydride-based methods.[1–3] Cyclizations are initiated by 2,6-dimethylbenzenesulfinyl chloride for the oxime substrates, and *tert*-butylsulfinyl chloride for the hydroxamic acids from −50°C to room temperature using diisopropylethylamine as a base. More conveniently, both types of cyclizations can be initiated by diethyl chlorophosphite under the same mild reaction conditions. This reagent generally produces selenide-trapped products in substantially higher yields than do the sulfinyl chlorides and gives similar yields of products when using diphenyl disulfide and TEMPO as the trapping reagents. Moreover, the chlorophosphite initiator is also preferable since it is a commercially available compound, and excess reagent can be easily removed due to its hydrolytic lability and water solubility. The reactions have been shown to work well for a wide variety of substrates involving 5-*exo* processes, but have been unsuccessful in analogous 6-*exo* cyclizations. We are continuing to explore improvements and applications of this methodolgy.

4. Experimental

4.1. General experimental

Reactions were run under an atmosphere of argon. Flash column chromatography was performed using E. Merck Silica Gel 60 (70–230 mesh). Preparative TLC was done with EM Silica Gel 60 PF254. THF was distilled from sodium/benzophenone ketyl. Methylene chloride was distilled from calcium hydride. Reactions run under high pressure were performed in a LECO model PG-200-HPC apparatus.

4.1.1. 2-(3-Methylbut-2-enyl)-cyclohexanone oxime (16). To a solution of cyclohexanone oxime (1.24 g, 11.0 mmol) in dry THF (40 mL) at −78°C was added *n*-BuLi (11.0 mL, 2 M solution in hexane) over 10 min. The resulting mixture was stirred in an ice bath for 20 min, recooled to −78°C and

4-bromo-2-methyl-2-butene (1.27 mL, 11 mmol) was added. The mixture was warmed to rt slowly and stirred for 1 h. The solution was washed with water, brine, dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by flash column chromatography (20% EtOAc/hexanes) to afford the ketoxime olefin **16** as a pale yellow solid (1.63 g, 82%): mp 68–69°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.12–5.07 (m, 1H), 2.85–2.81 (m, 1H), 2.38–2.29 (m, 1H), 2.22–2.10 (m, 3H), 2.00–1.82 (m, 1H), 1.73–1.36 (m, 5H), 1.69 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 162.6, 132.8, 122.4, 42.5, 32.2, 29.3, 26.1, 25.7, 24.0, 23.5, 17.9; HRMS ($C_{11}H_{19}NO$) calcd 182.1545 (MH^+), found 182.1550.

4.1.2. 2,6-Dimethylbenzenesulfinyl chloride. Excess sulfur dioxide was bubbled through a solution of 2,6-dimethylbenzenemagnesium bromide (20 mL, 1.0 M in THF, Aldrich) at 0°C in a fume hood allowing for adequate venting of excess SO_2. After 2–3 h, the reaction mixture was diluted with ice-cold 5% HCl (20 mL) and the aqueous layer was then extracted with 20 mL of methylene chloride. The organic extract was dried over $MgSO_4$, and concentrated in vacuo to afford 2,6-dimethylbenzenesulfinic acid as a white solid (3.3 g, 95%) which was used without further purification.

To a solution of 2,6-dimethylbenzenesulfinic acid (3.3 g, 19.0 mmol) in 7 mL of THF was added dropwise thionyl chloride (1.70 mL, 22.8 mmol) at rt. After 3 h, the solvent and excess thionyl chloride were evaporated in vacuo. The resulting 2,6-dimethylbenzenesulfinyl chloride (3.4 g, 95%) was used without further purification (dark green liquid). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35 (br t, J=7.6 Hz, 1H), 7.13 (br d, J=7.6 Hz, 2H), 2.66 (s, 6H).

4.2. General procedure for cyclization of oximes using 2,6-dimethylbenzenesulfinyl chloride

To a solution of the oxime (0.30 mmol)[13] and radical trap (TEMPO: 70 mg, 0.45 mmol; diphenyl diselenide: 187 mg, 0.60 mmol; diphenyl disulfide: 2.3 g, 6.0 mmol; cyclohexadiene: 8.5 mL, 9.0 mmol) in methylene chloride (7.5 mL) at −50°C were added successively diisopropylethylamine (0.105 mL, 0.60 mmol) and 2,6-dimethylbenzenesulfinyl chloride (113 mg, 0.60 mmol). The mixture was then warmed slowly to rt, and stirred for 5 h. The solution was concentrated and the residue was purified by flash column chromatography (20–100% EtOAc/hexanes gradient) to give the cyclization product as a yellow oil. Isolated yields are listed in Table 1.

4.3. General procedure for the cyclization of oximes using diethyl chlorophosphite

The oxime (0.3 mmol) was dissolved in CH_2Cl_2 (6 mL) with either $(PhSe)_2$ (0.6 mmol), $(PhS)_2$ (3–6 mmol), or TEMPO (0.6 mmol) and cooled to −50°C. DIEA (0.8 mmol) followed by $(EtO)_2PCl$ (0.38 mmol, Aldrich, 98% purity) were then slowly added. The solution was warmed to rt over 1 h and stirred for an additional 1 h. The volatile organics were removed under reduced pressure and the residue was purified by flash silica gel chromatography (hexanes-1/1 EtOAc/hexanes) to afford the desired cyclization products. Isolated yields are listed in Table 1.

4.3.1. 2-Phenylselanylmethyl-3,3a,4,5,6,7-hexahydro-2*H*-indole (12a). (3:2 Mixture of diastereoisomers): ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.58–7.54 (m, 2H), 7.29–7.24 (m, 3H), 4.38 (m, 0.4H), 4.10 (m, 0.6H), 3.44 (dd, J=11.8, 5.4 Hz, 0.6H), 3.25 (dd, J=12.2, 5.0 Hz, 0.4H), 3.05 (dd, J=11.8, 8.2 Hz, 0.6H), 2.94 (dd, J=12.2, 7.8 Hz, 0.4H), 2.78–2.54 (m, 2H), 2.40 (ddd, J=12.8, 9.1, 7.3 Hz, 0.6H), 2.21–1.97 (m, 3H), 1.88–1.78 (m, 1H), 1.68 (ddd, J=13.2, 8.7, 6.8 Hz, 0.4H), 1.50–1.09 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.5, 179.9, 132.3, 132.3, 130.6, 129.0, 126.6, 70.6, 70.5, 48.8, 48.0, 36.7, 34.9, 34.8, 34.6, 34.2, 31.9, 31.7, 27.0, 26.5, 25.3, 25.1; HRMS ($C_{15}H_{19}NSe$) calcd 292.0769 (MH^+), found 292.0760.

4.3.2. 2-Phenylsulfanylmethyl-3,3a,4,5,6,7-hexahydro-2*H*-indole (12b). (3:2 Mixture of diastereoisomers): ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.32–7.28 (m, 2H), 7.21–7.16 (m 2H), 7.08 (br t, J=7.3 Hz, 1H), 4.21 (m, 0.4H), 3.97 (m, 0.6H), 3.40 (dd, J=12.6, 5.4 Hz, 0.6H), 3.20 (dd, J=12.8, 4.7 Hz, 0.4H), 2.89 (dd, J=12.6, 8.2 Hz, 0.6H), 2.76 (dd, J=12.8, 8.0 Hz, 0.4H), 2.65–2.45 (m, 2H), 2.30 (ddd, J=12.9, 8.6, 7.5 Hz, 0.6H), 2.12–1.87 (m, 3H), 1.78–1.69 (m, 1H), 1.58 (ddd, J=13.3, 8.4, 6.6 Hz, 0.4H), 1.40–0.90 (m, 4H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 180.7, 180.1, 136.6, 136.6, 128.9, 128.8, 128.8, 125.7, 125.7, 69.8, 69.7, 48.6, 47.8, 40.3, 39.4, 36.1, 34.8, 34.7, 34.2, 31.8, 31.7, 26.9, 26.4, 25.2, 25.1; HRMS ($C_{15}H_{19}NS$) calcd 246.1316 (MH^+), found 246.1318.

4.3.3. 2-(2,2,6,6-Tetramethylpiperidin-1-yloxy)methyl-3,3a,4,5,6,7-hexahydro-2*H*-indole (12c). (3:2 Mixture of diastereoisomers): ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.15 (m, 0.4H), 4.03 (dd, J=8.2, 4.6 Hz, 0.6H), 4.01 (m, 0.6H), 3.89–3.82 (m, 1H), 3.76 (dd, J=8.6, 4.6 Hz, 0.4H), 2.66–2.58 (m, 2H), 2.20–2.03 (m, 3H), 1.94–1.86 (m, 1H), 1.78–1.68 (m, 1H), 1.48–0.92 (m, 22H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 180.1, 179.4, 79.7, 78.7, 70.3, 69.9, 59.8, 59.7, 48.7, 48.0, 39.6, 39.5, 34.8, 34.7, 33.1, 33.0, 32.9, 31.8, 31.7, 26.8, 26.7, 25.4, 25.3, 20.3, 17.1, 17.0; HRMS ($C_{18}H_{32}N_2O$) calcd 293.2593 (MH^+), found 293.2587. Anal. calcd for $C_{18}H_{32}N_2O$: C, 61.64; H, 6.55; N, 4.79;. Found: C, 61.42; H, 6.41; N, 4.71.

4.3.4. 5-Methyl-2-phenylselanyl-4-azatricyclo[4.2.1.0^{0,0}]-non-4-ene (13a). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.39 (m, 2H), 7.22–7.11 (m, 3H), 4.02 (d, J=4.6 Hz, 1H), 3.05 (m, 1H), 2.99 (s, 1H), 2.41–2.38 (m, 2H), 2.22 (br d, J=10.9 Hz, 1H), 1.96 (s, 3H), 1.68–1.58 (m, 2H), 1.28 (br d, J=12.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.2, 132.7, 130.5, 129.1, 126.8, 77.6, 52.3, 48.9, 48.0, 45.6, 37.4, 34.5, 19.4; HRMS ($C_{15}H_{17}NSe$) calcd 286.0664 (MH^+), found 286.0657.

4.3.5. 5-Methyl-2-phenylsulfanyl-4-azatricyclo[4.2.1.0^{0,0}]-non-4-ene (13b). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.26 (m, 4H), 7.14 (br t, J=7.2 Hz, 1H), 3.95 (d, J=4.4 Hz, 1H), 3.09 (m, 1H), 2.93 (s, 1H), 2.48–2.41 (m, 2H), 2.28 (br d, J=5.5 Hz, 1H), 2.03 (s, 3H), 1.67 (ddd, J=12.6, 10.3, 4.1 Hz, 1H), 1.62 (br d, J=11.0 Hz, 1H), 1.35 (br d, J=12.6 Hz, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 184.2, 136.1,

129.0, 129.0, 125.7, 77.2, 52.3, 52.2, 48.1, 44.9, 36.7, 34.2, 19.5; HRMS ($C_{15}H_{17}NS$) calcd 244.1160 (MH^+), found 244.1150.

4.3.6. 5-Methyl-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)-4-azatricyclo[4.2.1.0^{0,0}]non-4-ene (13c). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.03 (d, J=4.6 Hz, 1H), 3.39 (s, 1H), 2.99 (m, 1H), 2.72 (m, 1H), 2.30 (m, 1H), 1.99 (m, 1H), 1.95 (s, 3H), 1.43 (s, 6H), 1.13 (s, 6H), 1.57–1.13 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.3, 89.0, 79.4, 59.2, 50.8, 47.7, 44.9, 40.1, 34.9, 34.8, 32.7, 20.2, 19.2, 17.2; HRMS ($C_{18}H_{30}N_2O$) calcd 291.2436 (MH^+), found 291.2436.

4.3.7. 5-Methyl-2-(1-methyl-1-phenylselanylethyl)-3,4-dihydro-2*H*-pyrrole (14a). ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.66–7.64 (m, 2H), 7.36–7.25 (m, 3H), 4.04–4.00 (m 1H), 2.60–2.40 (m, 2H), 2.04 (s, 3H), 2.04–1.85 (m, 2H), 1.39 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 175.4, 138.4, 128.5, 128.3, 127.5, 82.1, 51.2, 39.4, 27.7, 26.4, 25.6, 19.8; HRMS ($C_{14}H_{19}NSe$) calcd 282.0760 (MH^+), found 282.0753.

4.3.8. 5-Methyl-2-(1-methyl-1-phenylsulfanylethyl)-3,4-dihydro-2*H*-pyrrole (14b). ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.56–7.54 (m, 2H), 7.34–7.29 (m, 3H), 3.99–3.94 (m, 1H), 2.55–2.41 (m, 2H), 2.04 (d, J=4.0 Hz, 3H), 1.90–2.05 (m, 2H), 1.30 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 175.5, 137.7, 131.7, 128.6, 128.4, 81.0, 52.5, 39.4, 27.0, 24.9, 24.6, 19.8; HRMS ($C_{14}H_{19}NS$) calcd 234.1316 (MH^+), found 234.1321. Anal. calcd for $C_{14}H_{19}NS$: C, 72.05; H, 8.21; N, 6.00. Found: C, 71.78; H, 8.15; N, 5.95.

4.3.9. 5-Methyl-2-[1-methyl-1-(2,2,6,6-tetramethylpiperidin-1-yloxy)ethyl]-3,4-dihydro-2*H*-pyrrole (14c). ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.30–4.25 (m, 1H), 2.49–2.44 (m, 2H), 2.01 (d, J=1.7 Hz, 3H), 2.04–1.92 (m, 2H), 1.51 (s, 3H), 1.50–1.42 (m, 4H), 1.31–1.24 (m, 2H), 1.15 (s, 3H), 1.13 (s, 3H), 1.07 (2, 3H), 1.06 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 174.5, 82.1, 80.5, 59.3, 40.9, 40.9, 39.3, 34.7, 24.4, 23.7, 22.3, 20.8, 20.4, 19.8, 17.1; HRMS ($C_{17}H_{32}N_2O$) calcd 281.2593 (MH^+), found 281.2599.

4.3.10. 4,4-Dimethyl-2-phenylselanylmethyl-3,4-dihydro-2*H*-pyrrole (15a). ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.58–7.49 (m, 2H), 7.32–7.16 (m, 4H), 4.31 (m, 1H), 3.35 (dd, J=11.9, 5.9 Hz, 1H), 3.01 (dd, J=11.9, 7.8 Hz, 1H), 1.96 (dd, J=12.9, 7.3 Hz, 1H), 1.40 (dd, J=12.9, 7.7 Hz, 1H), 1.19 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 175.3, 132.5, 130.4, 129.0, 126.8, 72.2, 49.9, 43.6, 34.3, 26.2, 24.8; HRMS ($C_{13}H_{17}NSe$) calcd 262.0664 (MH^+), found 262.0646.

4.3.11. 4,4-Dimethyl-2-phenylsulfanylmethyl-3,4-dihydro-2*H*-pyrrole (15b). ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.34 (br d, J=8.0 Hz, 2H), 7.25–7.20 (m, 3H), 7.10 (br t, J=7.3 Hz, 1H), 4.22 (m, 1H), 3.38 (dd, J=12.7, 5.6 Hz, 1H), 2.91 (dd, J=12.7, 8.1 Hz, 1H), 1.92 (dd, J=12.9, 7.4 Hz, 1H), 1.43 (dd, J=12.9, 7.7 Hz, 1H), 1.16 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 175.5, 136.4, 129.2, 128.9, 125.9, 71.5, 49.9, 42.9, 40.0, 26.2, 24.8; HRMS ($C_{13}H_{17}NS$) calcd 220.1160 (MH^+), found 220.1170.

4.3.12. 2-(1-Methyl-1-phenylselanylethyl)-3,3a,4,5,6,7-hexahydro-2*H*-indole (16a). (3:2 Mixture of diastereoisomers): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (br t, J=7.8 Hz, 2H), 7.29–7.18 (m, 3H), 4.10–4.03 (m, 0.4H), 3.88–3.80 (m, 0.6H), 2.60–2.45 (m, 2H), 2.20–2.02 (m, 3H), 1.96–1.87 (m, 1H), 1.76–1.68 (m, 1H), 1.58–1.14 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.7, 180.3, 168.5, 138.6, 133.3, 128.5, 128.5, 128.5, 128.4, 80.2, 80.0, 51.6, 50.5, 48.7, 48.2, 35.2, 34.3, 32.6, 32.0, 31.7, 27.9, 27.7, 27.1, 26.9, 26.7, 26.6, 26.5, 25.7, 25.3, 25.1; HRMS ($C_{17}H_{23}NSe$) calcd 318.1101 (MH^+), found 318.1080.

4.3.13. 2-(1-Methyl-1-phenylsulfanylethyl)-3,3a,4,5,6,7-hexahydro-2*H*-indole (16b). (3:2 Mixture of diastereoisomers): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (br t, J=7.2 Hz, 2H), 7.29–7.22 (m, 3H), 3.98–3.92 (m, 0.4H), 3.81–3.73 (m, 0.6H), 2.60–2.42 (m, 2H), 2.24 (m, 0.6H), 2.18–2.00 (m, 2.4H), 1.97–1.85 (m, 1H), 1.76–1.65 (m, 1H), 1.53–1.02 (m, 10H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 181.2, 180.1, 137.7, 137.6, 131.8, 131.6, 128.6, 128.6, 128.4, 128.3, 79.2, 79.0, 53.1, 51.9, 48.7, 48.2, 35.2, 34.3, 32.0, 31.8, 31.7, 31.5, 27.3, 27.1, 27.0, 26.6, 25.3, 25.1, 24.9, 23.8; HRMS ($C_{17}H_{23}NS$) calcd 274.1629 (MH^+), found 274.1651.

4.3.14. 2-[1-Methyl-1-(2,2,6,6-tetramethylpiperidin-1-yloxy)ethyl]-3,3a,4,5,6,7-hexahydro-dole (16c). (3:2 Mixture of diastereoisomers): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.37 (m, 0.4H), 4.14 (m, 0.6H), 2.68–2.62 (m, 1H), 2.56–2.47 (m, 1H), 2.33 (m, 0.6H), 2.22–2.06 (m, 2.4H), 2.02–1.97 (m, 1H), 1.84–1.76 (m, 1H), 1.58–0.92 (m, 28H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 180.2, 178.8, 80.6, 80.3, 80.1, 80.0, 59.3, 59.2, 48.7, 48.0, 40.9, 40.9, 35.4, 34.8, 34.8, 34.7, 34.6, 34.4, 32.0, 31.8, 31.1, 30.0, 27.2, 26.6, 25.5, 25.2, 24.5, 23.8, 22.7, 22.0, 20.8, 20.7, 20.4, 20.4, 17.1; HRMS ($C_{20}H_{36}N_2O$) calcd 321.2906 (MH^+), found 321.2924.

4.3.15. 2-Isopropyl-3,3a,4,5,6,7-hexahydro-2*H*-indole (17). (3:2 Mixture of diastereoisomers): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.90–3.80 (m, 0.4H), 3.55–3.49 (m, 0.6H), 2.70–2.45 (m, 3H), 2.18–2.04 (m, 3H), 2.00–1.89 (m, 1H), 1.82–1.71 (m, 2H), 1.50–1.08 (m, 3H), 1.04 (d, J=6.7 Hz, 1.8H), 0.93 (d, J=6.8 Hz, 1.2H), 0.85 (d, J=6.7 Hz, 1.8H), 0.79 (d, J=6.8 Hz, 1.2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.7, 178.4, 77.2, 76.8, 48.4, 48.1, 35.1, 34.7, 33.4 (2), 33.1, 31.8, 31.8, 31.5, 27.2, 26.6, 25.5, 25.2, 20.3, 19.5, 18.7, 18.2; HRMS ($C_{11}H_{19}N$) calcd 166.1596 (MH^+), found 166.1584.

4.4. General procedure for preparation of hydroxamic acids

To a solution of the alkenoic acid (1.0 mmol) in methylene chloride (2.50 mL) was added oxalyl chloride (0.174 mL, 2.0 mmol) and DMF (1 drop) at 0°C. The reaction mixture was stirred for 10 min at 0°C and for 1 h at rt. The solvent and excess reagents were removed by evaporation under reduced pressure, and the crude acid chloride obtained was added to an ice cooled suspension of N-substituted hydroxylamine hydrochloride (2.0 mmol), anhydrous Na_2CO_3 (0.33 g, 4.0 mmol) in dry ether (14 mL), containing 3 drops of pyridine. The reaction mixture was stirred

overnight at rt. Water was then added and the organic layer was separated, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (40% EtOAc/hexanes) to give the hydroxamic acid.

4.4.1. 2,2-Dimethylpent-4-enoic acid *N*-hydroxy-*N*-methyl amide (23). Colorless oil, 74%: ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.15 (br s, 1H), 5.67 (ddt, J=17.3, 10.0, 7.3 Hz, 1H), 5.04 (br s, 1H), 4.98 (br d, J=10.0 Hz, 1H), 3.23 (s, 3H), 2.40 (d, J=7.3 Hz, 2H), 1.20 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 176.5, 134.7, 117.5, 43.5, 42.2, 37.9, 25.1; HRMS ($C_8H_{15}NO_2$) calcd 158.1181 (MH^+), found 158.1183.

4.4.2. 2,2-Dimethylpent-4-enoic acid *N*-benzyl-*N*-hydroxy amide (26). White solid, 71%: mp 69–70°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.25–7.01 (m, 5H), 5.66 (ddt, J= 17.3, 10.0, 7.2 Hz, 1H), 4.96–4.91 (m, 2H), 4.74 (s, 2H), 2.34 (d, J=7.2 Hz, 2H), 1.19 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 176.1, 135.8, 134.7, 128.6, 128.1, 127.7, 117.6, 53.4, 44.1, 42.2, 25.5; HRMS ($C_{14}H_{19}NO_2$) calcd 234.1494 (MH^+), found 234.1477.

4.4.3. Bicyclo[2.2.1]hept-5-ene-2-carboxylic acid *N*-hydroxy-*N*-methyl amide (27). White solid, 66%: mp 65–66°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.23 (dd, J=5.5, 3.2 Hz, 1H), 5.98 (dd, J=5.5, 2.8 Hz, 1H), 3.40 (s, 3H), 3.15 (br s, 1H), 3.10–2.92 (m, 1H), 2.94 (br s, 1H), 2.00–1.90 (m, 1H), 1.50–1.30 (m, 3H).[13d]

4.4.4. 2-Cyclohex-2-enyl-*N*-hydroxy-*N*-methyl acetamide (28). Pale yellow oil, 67%: ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.21 (br s, 1H), 5.75–5.72 (m, 1H), 5.55 (br d, J=9.4 Hz, 1H), 3.37 (s, 3H), 2.67 (br s, 1H), 2.30 (br s, 2H), 1.98–1.25 (m, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 173.5, 130.5, 127.5, 38.2, 35.9, 31.8, 28.8, 24.9, 20.9; HRMS ($C_9H_{15}NO_2$) calcd 170.1181 (MH^+), found 170.1191.

4.4.5. Cyclohex-3-enecarboxylic acid *N*-hydroxy-*N*-methyl amide (29). Colorless oil, 84%: ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.70 (s, 2H), 3.39 (s, 3H), 2.65 (br s, 1H), 2.33–1.80 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 170.1, 126.5, 125.6, 125.0, 36.2, 35.9, 35.6, 27.2, 24.9, 24.7; HRMS ($C_8H_{13}NO_2$) calcd 156.1025 (MH^+), found 156.1025.

4.4.6. 2,2-Dimethylpent-4-enoic acid *N*-hydroxy-*N*-(3-methylbut-2-enyl) amide (30). Colorless oil, 60%: ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.75 (ddt, J=18.0, 9.1, 7.3 Hz, 1H), 5.23 (br t, J=6.8 Hz, 1H), 5.08–5.03 (m, 2H), 4.29 (d, J=6.8 Hz, 2H), 2.39 (d, J=7.3 Hz, 2H), 1.75 (s, 3H), 1.71 (s, 3H), 1.26 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 174.6, 137.8, 134.7, 117.9, 117.6, 47.8, 44.4, 41.7, 25.7, 25.6, 22.45, 18.0; HRMS ($C_{12}H_{21}NO_2$) calcd 212.1651 (MH^+), found 212.1641.

4.5. General procedure for cyclization of hydroxamic acids using *tert*-butylsulfinyl chloride

To a solution of the hydroxamic acid (0.30 mmol) and radical trap (TEMPO: 70 mg, 0.45 mmol; diphenyl diselenide: 187 mg, 0.60 mmol; diphenyl disulfide: 4.6 g, 12.0 mmol) in methylene chloride (15 mL) at −50°C was added successively diisopropylethylamine (0.131 mL, 0.75 mmol) and *tert*-butylsulfinyl chloride (63 mg, 0.45 mmol). The mixture was then warmed slowly to rt and stirred for about 5 h. The solution was concentrated and the residue was purified by flash column chromatography (20–50% EtOAc/hexanes gradient) to give the cyclization product as a yellow oil. Isolated yields are listed in Table 2.

4.6. General procedure for cyclization of hydroxamic acids using diethyl chlorophosphite

The hydroxamic acid (0.3 mmol) was dissolved in CH_2Cl_2 (10 mL) with either $(PhSe)_2$ (0.6 mmol), $(PhS)_2$ (3–6 mmol), or TEMPO (0.6 mmol) and cooled to −50°C. DIEA (0.8 mmol) followed by $(EtO)_2PCl$ (0.45 mmol, Aldrich, 98% purity) were then slowly added. The solution was warmed to rt over 1 h and stirred for an additional 1 h. The volatile organics were removed under reduced pressure and the residue was purified by flash column chromatography (20/80 EtOAc/hexanes-1/1 EtOAc/hexanes) to afford the desired γ-lactam. Isolated yields are listed in Table 2.

4.6.1. 1,3,3-Trimethyl-5-phenylselanylmethylpyrrolidin-2-one (23a). ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.53–7.50 (m, 2H), 7.30–7.26 (m, 3H), 3.64 (m, 1H), 3.26 (dd, J=12.2, 3.2 Hz, 1H), 2.91 (dd, J=12.2, 8.5 Hz, 1H), 2.75 (s, 3H), 2.10 (dd, J=12.2, 7.3 Hz, 1H), 2.91 (dd, J=12.2, 7.3 Hz, 1H), 1.20 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 180.0, 133.2, 129.3, 129.3, 127.5, 76.6, 56.3, 40.7, 40.2, 32.4, 28.0, 25.8, 25.5; HRMS ($C_{14}H_{19}NOSe$) calcd 294.0737 (MH^+), found 294.0716.

4.6.2. 1,3,3-Trimethyl-5-phenylsulfanylmethylpyrrolidin-2-one (23b). ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.38–7.22 (m, 5H), 3.64–3.59 (m, 1H), 3.31 (dd, J=12.9, 3.5 Hz, 1H), 2.93 (dd, J=12.9, 8.1 Hz, 1H), 2.79 (s, 3H), 2.10 (dd, J=13.0, 7.5 Hz, 1H), 1.75 (dd, J=13.0, 7.5 Hz, 1H), 1.21 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 180.0, 135.5, 130.1, 129.1, 126.7, 77.8, 55.9, 40.1, 39.9, 38.4, 28.2, 25.9, 25.5; HRMS ($C_{14}H_{19}NOS$) calcd 250.1266 (MH^+), found 250.1289.

4.6.3. 1,3,3-Trimethyl-5-(2,2,6,6-tetramethylpiperidin-1-yloxy)methyl-pyrrolidin-2-one (23c). ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.79 (AB_q J=9.8 Hz, each peak further split, d, J=6.9, 3.7 Hz, 2H), 3.64–3.57 (m, 1H), 2.92 (s, 3H), 1.96 (dd, J=12.8, 7.9 Hz, 1H), 1.55 (dd, J=12.8, 7.0 Hz, 1H), 1.46–1.41 (m, 4H), 1.34–1.28 (m, 2H), 1.18 (s, 3H), 1.14 (s, 6H), 1.11 (s, 3H), 1.09 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 180.0, 79.7, 59.9, 55.9, 39.9, 39.6, 37.3, 33.1, 32.9, 29.3, 25.9, 25.4, 20.3, 20.1, 16.9; HRMS ($C_{17}H_{32}N_2O_2$) calcd 297.2542 (MH^+), found 297.2563.

4.6.4. *N*-(2,2-Dimethylpent-4-enoyl)-*N*-methyl-*t*-butylsulfonamide (24). Mixture of rotamers: ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.77 (ddt, J=17.3, 10.1, 7.1 Hz, 1H), 5.13 (br s, 1H), 5.08 (m, 1H), 3.82 (s, 0.7H), 3.41 (s, 2.3H), 2.44–2.39 (m, 2H), 1.56 (s, 2.1H), 1.49 (s, 6.9H), 1.33 (s, 1.4H), 1.29 (s, 4.6H); HRMS ($C_{12}H_{23}NO_3S$) calcd 262.1477 (MH^+), found 262.1495.

4.6.5. 1-Benzyl-3,3-dimethyl-5-phenylselanylmethylpyrrolidin-2-one (26a). ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.28–7.12 (m, 10H), 4.93 (d, J=15.0 Hz, 1H), 3.78 (d, J=15.0 Hz, 1H) 3.48–3.38 (m, 1H), 3.31 (dd, J=12.3, 3.1 Hz, 1H), 2.72 (dd, J=12.3, 9.0 Hz, 1H), 1.99 (dd, J=12.9, 7.2 Hz, 1H), 1.59 (dd, J=12.9, 7.7 Hz, 1H), 1.18 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 180.1, 136.3, 132.6, 129.3, 129.2, 128.7, 127.9, 127.5, 127.1, 53.1, 44.2, 40.6, 40.2, 31.7, 25.5, 25.3; HRMS ($C_{20}H_{23}NOSe$) calcd 374.1023 (MH^+), found 374.1027.

4.6.6. 1-Benzyl-3,3-dimethyl-5-phenylsulfanylmethylpyrrolidin-2-one (26b). ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.28–7.02 (m, 10H)), 4.98 (d, J=15.1 Hz, 1H), 3.81 (d, J=15.1 Hz, 1H) 3.50–3.39 (m, 1H), 3.17 (dd, J=13.1, 3.2 Hz, 1H), 2.70 (dd, J=13.1, 8.7 Hz, 1H), 1.96 (dd, J=12.9, 7.3 Hz, 1H), 1.59 (dd, J=12.9, 7.5 Hz, 1H), 1.19 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 180.2, 136.4, 135.4, 129.3, 129.0, 128.8, 128.0, 127.7, 126.4, 52.6, 44.4, 40.2, 39.9, 37.5, 25.6, 25.3; HRMS ($C_{20}H_{23}NOS$) calcd 326.1579 (MH^+), found 326.1605.

4.6.7. 1-Benzyl-3,3-dimethyl-5-(2,2,6,6-tetramethylpiperidin-1-yloxy)methylpyrrolidin-2-one (26c). ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.32–7.22 (m, 5H), 5.15 (d, J=14.7 Hz, 1H), 4.10 (d, J=14.7 Hz, 1H), 3.92 (dd, J=9.6, 6.5 Hz, 1H), 3.78 (dd, J=9.6, 4.3 Hz, 1H), 3.55 (m, 1H), 1.93 (dd, J=12.9, 7.9 Hz, 1H), 1.62 (dd, J=12.9, 6.9 Hz, 1H), 1.48–1.33 (m, 6H), 1.25 (s, 3H), 1.25–1.09 (m, 12H), 1.13 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 180.1, 136.9, 128.4, 128.1, 127.2, 79.6, 59.9, 52.5, 44.9, 39.9, 39.6, 37.5, 33.0, 32.9, 25.7, 25.4, 20.4, 20.2, 16.9; HRMS ($C_{23}H_{36}N_2O_2$) calcd 373.2855 (MH^+), found 373.2852.

4.6.8. 4-Methyl-2-phenylselanyl-4-azatricyclo[4.2.1.0^{0,0}]nonan-5-one (27a). ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.59–7.58 (m, 2H), 7.32–7.28 (m, 3H), 3.52 (d, J=4.7 Hz, 1H), 3.02 (br s, 2H), 2.52–2.49 (m, 1H), 2.36 (s, 3H), 2.34–2.37 (m, 1H), 2.12 (br, d, J=10.9 Hz, 1H), 1.90–2.00 (m, 1H), 1.00–1.10 (m, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 179.0, 135.2, 129.3, 128.5, 128.2, 68.7, 49.7, 45.0, 43.5, 41.4, 35.8, 35.6, 28.1; HRMS ($C_{15}H_{17}NOSe$) calcd 308.0554 (MH^+), found 308.0561.

4.6.9. 4-Methyl-2-phenylsulfanyl-4-azatricyclo[4.2.1.0^{0,0}]nonan-5-one (27b). ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.39–7.36 (m, 2H), 7.29–7.20 (m, 3H), 3.30 (d, J=4.8 Hz, 1H), 2.96 (br t, J=4.6 Hz, 1H), 2.88 (br s, 1H), 2.46–2.44(m, 1H), 2.40 (s, 3H), 2.35–2.31 (m, 1H), 2.21 (br, d, J=11.0 Hz, 1H), 1.94–1.85 (m, 1H), 1.55–1.45 (m, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 179.0, 133.9, 132.8, 129.1, 127.7, 68.1, 54.5, 44.8, 43.0, 41.6, 35.1, 34.9, 28.3; HRMS ($C_{15}H_{17}NOS$) calcd 260.1109 (MH^+), found 260.1106.

4.6.10. 4-Methyl-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)-4-azatricyclo[4.2.1.0^{0,0}]nonan-5-one (27c). ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.58 (d, J=4.0 Hz, 1H), 3.54 (s, 1H), 2.92–2.86 (m, 1H), 2.82 (s, 3H), 2.68 (s, 1H), 2.28 (br d, J=10.4 Hz, 1H), 1.90–1.80 (m, 2H), 1.48–1.32 (m, 7H), 1.20–1.10 (m, 13H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 179.4, 87.9, 68.3, 59.7, 43.7, 43.3, 41.6, 40.1, 35.1, 34.7, 33.7, 32.8, 28.9, 20.2, 17.1; HRMS ($C_{18}H_{30}N_2O_2$) calcd 307.2386 (MH^+), found 307.2388.

4.6.11. 1-Methyl-7-phenylselanyloctahydroindol-2-one (28a). ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.60–7.58 (m, 2H), 7.36–7.28 (m, 3H), 3.56–3.49 (m, 2H), 2.86 (s, 3H), 2.59–2.52 (m, 1H), 2.31 (dd, J=16.2, 7.1 Hz, 1H), 2.13 (dd, J=16.2, 4.9 Hz, 1H), 1.81–1.72 (m, 2H), 1.64–1.52 (m, 2H), 1.48–1.32 (m, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 175.8, 134.6, 129.3, 128.8, 128.0, 63.1, 43.0, 37.4, 31.8, 28.7, 28.4, 27.2, 20.5; HRMS ($C_{15}H_{19}NOSe$) calcd 308.0722 (MH^+), found 308.0737.

4.6.12. 1-Methyl-7-phenylsulfanyloctahydroindol-2-one (28b). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.34 (m, 2H), 7.24–7.12 (m, 3H), 3.38(dd, J=5.8, 5.7 Hz, 1H), 3.32–3.28 (m, 1H), 2.89 (s, 3H), 2.53–2.49 (m, 1H), 2.23 (dd, J=16.0, 7.2 Hz, 1H), 2.10 (dd, J=16.0, 6.5 Hz, 1H), 1.72–1.49 (m, 4H), 1.41–1.32 (m, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 175.5, 134.1, 132.1, 129.1, 127.4, 62.6, 47.5, 36.7, 32.1, 29.4, 28.5, 26.9, 19.5; HRMS ($C_{15}H_{19}NOS$) calcd 262.1266 (MH^+), found 262.1242.

4.6.13. 1-Methyl-7-(2,2,6,6-tetramethylpiperidin-1-yloxy)octahydroindol-2-one (28c). ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.82 (ddd, J=7.3, 7.2, 3.5 Hz, 1H), 3.28 (dd, J=7.2, 7.1 Hz, 1H), 2.97 (s, 3H), 2.55–2.51 (m, 1H), 2.16–2.06 (m, 2H), 1.61–0.96 (m, 24H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 174.8, 83.0, 64.3, 58.7, 40.1 (br), 35.7, 34.2, 33.8, 33.6, 30.2, 27.2, 26.5, 20.8, 20.5, 18.9, 17.1; HRMS ($C_{18}H_{32}N_2O_2$) calcd 309.2542 (MH^+), found 309.2559.

4.6.14. 6-Methyl-4-phenylselanyl-6-azabicyclo[3.2.1]octan-7-one (29a). (2:1 Mixture of *exo*/*endo* isomers): *Exo* isomer: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.58–7.53 (m, 2H), 7.32–7.28 (m, 2H), 3.76–3.74 (m, 1H), 3.57–3.55 (m, 1H), 2.82 (s, 3H), 2.47 (br s, 1H), 2.10–2.03 (m, 2H), 1.97–1.75 (m, 4H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 177.1, 134.1, 129.3, 127.9, 61.6, 40.3, 39.7, 33.3, 27.4, 25.5, 22.7. *endo* Isomer: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.60–7.53 (m, 2H), 7.40–7.32 (m, 3H), 3.76 (d, J=5.7 Hz, 1H), 3.44 (dd, J=11.9, 5.3 Hz, 1H), 3.12 (s, 3H), 2.47 (br s, 1H), 2.30–2.12 (m, 2H), 1.85–1.54 (m, 4H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 176.8, 134.3, 129.3, 129.3, 127.8, 62.0, 43.6, 40.2, 39.5, 30.6, 27.1, 27.1; HRMS ($C_{14}H_{17}NOSe$) calcd 292.0581 (MH^+), found 292.0574.

4.6.15. 6-Methyl-4-phenylsulfanyl-6-azabicyclo[3.2.1]octan-7-one (29b). (1:1 Mixture of diastereoisomers): *Exo* isomer: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.43–7.40 (m, 2H), 7.34–7.28 (m, 3H), 3.68–3.66 (m, 1H), 3.54 (br s, 1H), 2.85 (s, 3H), 2.48–2.46 (m, 1H), 2.21–1.71 (m, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 177.2, 135.2, 131.5, 129.4, 127.3, 61.0, 42.8, 40.3, 32.0, 27.5, 24.7, 22.3. *endo* Isomer: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.43–7.41 (m, 2H), 7.35–7.27 (m, 3H), 3.70 (d, J=5.8 Hz, 1H), 3.41–3.38 (m, 1H), 3.12 (s, 3H), 2.46 (br s, 1H), 2.30–1.92 (m, 3H), 1.64–1.50 (m, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 176.7, 134.6, 131.7, 129.2, 127.3, 61.0, 48.2, 40.1, 38.4, 30.7, 26.3, 26.1; HRMS ($C_{14}H_{17}NOS$) calcd 248.1109 (MH^+), found 248.1104.

4.6.16. 6-Methyl-4-(2,2,6,6-tetramethylpiperidin-1-yloxy)-6-azabicyclo[3.2.1]octan-7-one (29c). (1:1 Mixture of diastereoisomers): ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.05–4.00 (m, 0.5H), 3.89–3.81 (m, 1H), 3.78–3.71 (m, 0.5H), 2.97 (s, 1.5H), 2.80 (s, 1.5H), 2.40 (br s, 0.5H), 2.38 (br s,

0.5H), 2.35–1.12 (m, 24H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 177.7, 177.1, 82.8, 75.7, 62.2, 60.0, 59.9, 40.2, 40.2, 35.9, 34.1, 31.0, 29.2, 27.8, 27.4, 25.1, 24.1, 22.7, 20.2, 17.1, 17.0; HRMS ($C_{17}H_{30}N_2O_2$) calcd 295.2386 (MH^+), found 295.2411.

4.6.17. 2,2-Dimethyl-6-(1-methyl-1-methylselanylethyl)-hexahydropyrrolizin-3-one (32). (2:1 Mixture of diastereoisomers): Major isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (br d, J=7.9 Hz, 2H), 7.38–7.28 (m, 3H), 3.96–3.88 (m, 1H), 3.89 (dd, J=12.2, 8.3 Hz, 1H), 2.91 (dd, J=12.2, 8.3 Hz, 1H), 2.39 (dddd, J=9.7, 8.3, 8.3, 7.1 Hz, 1H), 2.21–2.07 (m, 1H), 2.17 (dd, J=12.3, 6.5 Hz, 1H), 1.59 (ddd, J=13.3, 9.7, 6.6 Hz, 1H), 1.47 (dd, J=12.3, 8.6 Hz, 1H), 1.34 (s, 6H), 1.21 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.5, 138.4, 128.8, 126.8, 56.4, 50.4, 48.7, 45.2, 44.1, 34.6, 28.3, 27.7, 25.1, 24.6. Minor isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (br d, J=6.9 Hz, 2H), 7.38–7.28 (m, 3H), 3.88-3.80 (m, 1H), 3.45 (dd, J=11.7, 9.1 Hz, 1H), 3.20 (dd, J=11.7, 9.1 Hz, 1H), 2.65 (dddd, J=11.7, 9.1, 9.1, 6.3 Hz, 1H), 2.15–2.09 (m, 1H), 2.12 (dd, J=12.3, 6.1 Hz, 1H), 1.65–1.57 (m, 1H), 1.61 (dd, J=12.3, 8.1 Hz, 1H), 1.35 (s, 3H), 1.34 (s, 3H), 1.20 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.5, 138.4, 128.8, 127.0, 58.0, 52.4, 47.6, 45.6, 43.5, 43.1, 35.6, 27.7, 27.4, 25.2, 24.9; HRMS ($C_{18}H_{25}NOSe$) calcd 352.1180 (MH^+), found 352.1170.

4.6.18. 6-Methyl-6-azabicyclo[3.2.1]oct-3-en-7-one (33). To a solution of the selenide **29a** (60 mg, 0.20 mmol) in methylene chloride (10 mL) at 0°C was added 30% H_2O_2 (0.18 mL) dropwise. The solution was slowly warmed to rt and 3 drops of pyridine were added. After stirring for 3 h, the mixture was washed with brine, dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography (60% EtOAc/hexanes) to provide alkene **33** (25 mg, 90%). ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.25–6.18 (m, 1H), 5.70–5.64 (m, 1H), 3.55 (t, J=4.9 Hz, 1H), 2.78 (s, 3H), 2.63 (s, 1H), 2.29 (s, 2H), 2.26 (ddd, J=10.0, 5.0, 5.0 Hz, 1H), 1.89 (d, J=10.3 Hz, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 178.0, 130.3, 129.1, 54.9, 39.8, 33.6, 28.4, 28.1; HRMS ($C_8H_{11}NO$) calcd 138.0919 (MH^+), found 138.0918.

4.6.19. *N*-Hydroxy-*N*-isopropylacrylamide (38). To a solution of *N*-isopropyl hydroxylamine hydrochloride (1.75 g, 15.7 mmol) and anhydrous sodium carbonate (3.00 g, 36.1 mmol) in dry ether (150 mL) at 0°C was added acryloyl chloride (1.00 mL, 12.3 mmol) and anhydrous pyridine (3 drops). The reaction mixture was stirred overnight at rt. Water was then added and the organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (40% EtOAc/hexanes) to give hydroxamic acid **38** as a pale yellow oil (1.25 g, 80%). ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.76 (br s, 1H), 6.85–6.37 (m, 2H), 5.67 (br s, 1H), 4.70–4.27 (m, 1H), 1.30–1.17 (m, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 165.9, 160.5, 128.5, 127.9, 127.1, 123.8, 50.7, 47.4, 19.9, 18.8; HRMS ($C_6H_{11}NO_2$) calcd 130.0868 (MH^+), found 130.0867.

4.6.20. 2-Methoxycyclohex-3-enecarboxylic acid *N*-hydroxy-*N*-isopropyl amide (39). A solution of hydroxamic acid **38** (0.32 g, 2.5 mmol) and 1-methoxybutadiene (**37**, Aldrich, 0.30 mL, 3.0 mmol) in 5 mL of methylene chloride was kept at rt and 12 Kbar pressure for 2 days. The solution was then evaporated and the residue was purified by flash column chromatography (50% EtOAc/hexanes) to yield the adduct **39** (0.35 g, 65%) as a pale yellow oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.83 (br s, 1H), 5.84 (s, 2H), 4.62 (br s, 1H), 4.17 (br s, 1H), 3.26 (s, 3H), 3.10–3.05 (m, 1H), 2.10–1.52 (m, 4H), 1.10 (d, J=6.8 Hz, 3H), 1.09 (d, J=6.8 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 173.5, 131.4, 124.9, 72.2, 56.9, 47.2, 42.5, 24.9, 19.2, 18.7, 18.5; HRMS ($C_{11}H_{19}NO_3$) calcd 214.1443 (MH^+), found 214.1426.

4.6.21. 6-Isopropyl-8-methoxy-4-phenylselanyl-6-azabicyclo[3.2.1]octan-7-one (40). *Method A*: To a solution of the hydroxamic acid **39** (63 mg, 0.30 mmol) and diphenyl diselenide (0.19 g, 0.60 mmol) in methylene chloride (15 mL) at −50°C was added diisopropylethylamine (0.13 mL, 0.75 mmol) and *tert*-butylsulfinyl chloride (63 mg, 0.45 mmol). The mixture was then warmed slowly to rt, and stirred for 5 h. The solution was evaporated in vacuo and the residue was purified by flash column chromatography (20–50% EtOAc/hexanes gradient) to give the cyclization product **40** (32 mg, 30%) as a yellow oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.58–7.55 (m, 2H), 7.32–7.30 (m, 3H), 4.33 (septet, J=6.8 Hz, 1H), 3.90 (br d, J=3.6 Hz, 1H), 3.88 (s, 1H), 3.64–3.61 (m, 1H), 3.30 (s, 3H), 2.55 (br s, 1H), 2.12–1.75 (m, 4H), 1.15 (d, J=6.8 Hz, 3H), 1.09 (d, J=6.8 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 173.6, 134.1, 129.4, 129.3, 128.0, 83.4, 59.6, 55.6, 46.6, 42.9, 42.8, 24.5, 21.7, 21.5, 20.3; HRMS ($C_{17}H_{23}NO_2Se$) calcd 354.0972 (MH^+), found 354.0986. *Method B*: To a solution of the hydroxamic acid **39** (53 mg, 0.25 mmol) and diphenyl diselenide (156 mg, 0.50 mmol) in CH_2Cl_2 (8 mL) at −50°C was added diisopropylethylamine (115 μL, 0.66 mmol) followed by diethyl chlorophosphite (56 μL, 0.39 mmol). The solution was stirred and slowly warmed to rt over 2 h. The volatile organics were removed in vacuo and the residue was purified by flash column chromatography (20% EtOAc: hexanes to 50% EtOAc: hexanes) to afford the bicyclic lactam **40** (62 mg, 70%) as a yellow oil.

4.6.22. 6-Isopropyl-8-methoxy-6-azabicyclo[3.2.1]oct-3-en-7-one (41). To a solution of the selenide **40** (70 mg, 0.20 mmol) in 10 mL of methylene chloride at 0°C was added 30% H_2O_2 (0.18 mL) dropwise. The solution was warmed to rt slowly and anhydrous pyridine (3 drops) was added. After stirring for 3 h, the mixture was washed with brine, dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography (50–100% EtOAc/hexanes gradient) to provide olefin **41** (53 mg, 90%) as a colorless oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.10 (ddt, J=9.4, 5.4, 2.0 Hz, 1H), 5.63 (dt, J=9.4, 3.2 Hz, 1H), 4.32 (septet, J=6.8 Hz, 1H), 3.79 (s, 1H), 3.77 (d, J=5.4 Hz, 1H), 3.36 (s, 3H), 2.69–2.67 (m, 1H), 2.52–2.36 (m, 2H), 1.12 (d, J=6.8 Hz, 3H), 1.11 (d, J=6.8 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 173.9, 131.0, 128.4, 83.2, 55.8, 51.4, 45.4, 42.2, 28.3, 22.2, 20.5; HRMS ($C_{11}H_{17}NO_2$) calcd 196.1338 (MH^+), found 196.1334.

4.6.23. 8-Hydroxy-6-isopropyl-6-azabicyclo[3.2.1]oct-3-en-7-one (35). To a solution of methyl ether **41** (20 mg,

0.10 mmol) in 2 mL of methylene chloride was added BBr_3 (1.00 mL, 1 M solution in CH_2Cl_2) at −78°C. After 1 h the mixture was warmed to −20°C, and monitored by TLC. After completion of the reaction (3 h), the mixture was diluted with saturated $NaHCO_3$ solution. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (50–100% EtOAc/hexanes gradient) to afford the alcohol **35** (15 mg, 83%) as a white solid: mp 86–88°C; ^1H NMR (360 MHz, $CDCl_3$) δ 6.10 (ddt, J=9.2, 5.5, 2.2 Hz, 1H), 5.60 (dt, J=9.2, 3.2 Hz, 1H), 4.32 (septet, J=6.9 Hz, 1H), 4.22 (s, 1H), 3.64 (d, J=5.5 Hz, 1H), 2.63 (s, 1H), 2.45–2.43 (m, 2H), 1.16 (d, J=6.9 Hz, 3H), 1.14 (d, J=6.9 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 174.4, 131.0, 127.9, 74.7, 56.4, 48.4, 42.6, 28.4, 22.1, 20.4; HRMS ($C_{10}H_{15}NO_2$) calcd 182.1181 (MH^+), found 182.1199.

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