GENERATION AND CYCLIZATION OF NITRILIUM IONS FROM AMIDES

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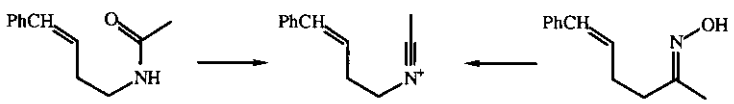
Abstract *- Amides are shown to be efficient precursors to nitrilium ions, which may cyclize onto styryl terminators to form pyrrolines. Comparison of several cyclization substrates defines the steric and stereoelectronic scope and limitations of the process. Appropriately functionalized pyrrolines may be reduced with chiral borohydrides and further elaborated to nonracemic pyrrolizidines and indolizidines.*

The cyclization of a nitrilium ion or imidate to form a heterocycle was first observed in the 19th century, but synthetically useful procedures have only emerged recently.[1] Our interest in the process developed out of a study of cationic cyclizations of alkenyl oximes.[2] Although the notion of generating a nitrilium ion (or imidate) from an oxime has some appeal because of the synthetic usefulness and general availability of oximes, the stereospecificity of the Beckmann rearrangement also introduces a serious limitation. Specifically, obtaining any given nitrilium ion from an oxime is predicated on the availability of the oxime *as a single geometric isomer*. Oximation of almost all dialkyl ketones gives rise to a mixture of both oxime geometric isomers, which are usually difficult to separate. Alkylation of oxime dianions can be used to stereospecifically synthesize some oximes, but this method is not useful for making substrates for Beckmann rearrangement–cyclizations. In spite of these limitations, the Beckmann rearrangement–cyclization has some useful applications.[1a]

In a preliminary communication, we showed that nitrilium ions may be prepared as efficiently from 2° amides as from oximes,[3] and we now detail the scope and the limitations of the process.

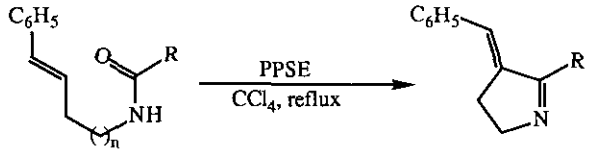


The styryl terminator was chosen for a number of reasons. Specifically, it was shown to be highly effective in oxime rearrangement cyclizations,[2c] and the conditions necessary to generate a nitrilium ion are rather severe, and terminators (e.g., allyl- or vinylsilanes) which might otherwise offer some advantages were not expected to survive.[4] Most amides were prepared by acylation of *E*-4-phenyl-3-butenylamine, which was best prepared by lithium aluminum hydride (LAH) reduction of 1-phenyl-4-nitrobutadiene (60% yield).[5]

We examined the cyclization of several amides with trimethylsilyl polyphosphate (PPSE)[6] in refluxing carbon tetrachloride. The results of this survey are listed in Table I. From entries *1–3*, it is apparent that the cyclization is highly efficient. In fact, it is noteworthy that there seems to be little steric effect exerted by the amide, as evidenced by the successful cyclization of pivalamide **3**. The first examples of functionalized nitrilium ion cyclizations in the aliphatic series are shown in entries *4* - *6*. That substrates containing esters and ethers cyclize at all is noteworthy, since oximes containing the same functional groups cyclized only in low (<10%) yield under similar conditions.[7] A substrate containing a benzyl ether (entry *7*) was destroyed under the reaction conditions, reinforcing our notion that only robust terminators will survive the reaction conditions. Chloroacetamide **8** survived the cyclization, while chloropropionamide **10** did not.

Two substrates tested were recovered unchanged: dichloroacetamide **9** and acetamide **11**, the homolog of **1**. In the case of the dichloroacetamide **9**, the failure is probably due to inductive electron withdrawal by the geminal chlorines. This electron withdrawal would destabilize the forming nitrilium ion, raising the activation energy for its formation. The failure of **11** to cyclize results from a failure to achieve the appropriate orbital overlap geometry.

Table I. Survey of Amide Substrates in Nitrilium Ion Cyclizations

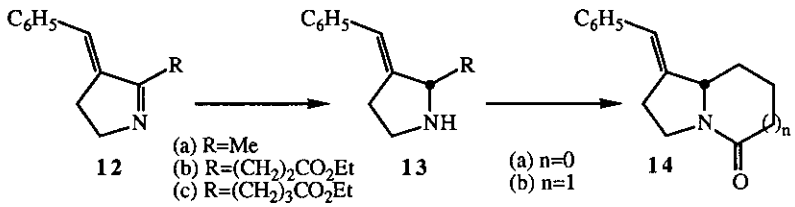


Entry	n	R, substrate	Yield %)
1	1	Me, **1**	88
2	1	i-Pr, **2**	90
3	1	t-Bu, **3**	81
4	1	$(CH_2)_2CO_2Et$, **4**	60
5	1	$(CH_2)_3CO_2Et$, **5**	60
6	1	$(CH_2)_2OMe$, **6**	55
7	1	$(CH_2)_2OBn$, **7**	0
8	1	CH_2Cl, **8**	62
9	1	$CHCl_2$, **9**	0
10	1	$(CH_2)_2Cl$, **10**	0
11	2	Me, **11**	0

From the beginnings of our work in nitrilium ion chemistry, we have been cognizant of the developments in related iminium ion chemistry. Within the context of heterocycle formation, we note one potentially important difference between the two, which arises because of the difference in oxidation state of the cationic carbon. Iminium ion cyclizations generate a new stereocenter, but the product is a mixture of epimers (enantiomers for an achiral

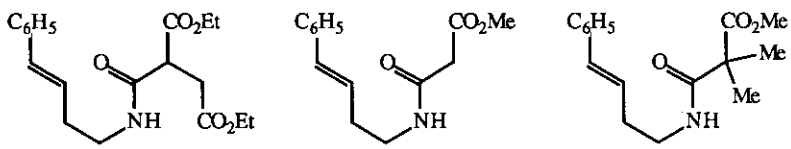
substrate). In contrast, the corresponding nitrilium ion, whose cationic carbon is in a higher oxidation state, cyclizes to an achiral product. Asymmetric reduction of the pyrroline affords access to nonracemic products. For example, reduction of **12a** with benzyloxycarbonylproline modified sodium borohydride[8] affords pyrrolidine *S*-**13a** in 95% yield and 50% enantiomeric excess.[9]

A similar reduction of appropriately functionalized pyrrolines affords nonracemic azabicyclics. Thus, **12b** affords pyrrolizidinone **14a** (78% yield) and **12c** gives indolizidinone **14b** (77% yield). The optical purity of **14a-b** was not determined, but is assumed to be comparable in magnitude and absolute configuration to **13a.**



12 **13** **14**

For the possible preparation of more elaborate pyrrolizidines or indolizidines, we tested diester **15** as a cyclization substrate. Treatment of amide **15** with PPSE resulted in destruction of starting material and production of an intractable mixture in which none of the desired pyrroline could be detected. Simpler substrates, such as the monoamide monoester of malonic acid, **16**, and the monoamide monoester of 2,2-dimethylmalonic acid, **17**, also failed to cyclize. In the latter case, traces of a cyclization product could be detected, but not in amounts sufficient for characterization. It appears that the nitrilium ion cyclization is occurring in these cases, but that the benzylic cation is trapped by the malonate oxygen and destroyed.



15 **16** **17**

Summary: Secondary amides are efficient precursors to nitrilium ions, which may cyclize onto styryl terminators to form achiral pyrrolines (5-exo mode). It is noteworthy that there is little steric demand placed on the amide portion of the substrate, although electron withdrawing substituents tend to inhibit nitrilium ion formation. A severe stereoelectronic requirement is seen in the failure of **11** to cyclize (6-exo mode) due to its inability to achieve the correct orbital overlap geometry. Notwithstanding the above limitations, appropriately functionalized pyrrolines may be reduced with chiral borohydrides and further elaborated to nonracemic pyrrolizidines and indolizidines.

EXPERIMENTAL

1-Phenyl-4-nitrobutadiene was prepared from *trans*-cinnamaldehyde using Kochetkov's method.[5] Yield 60%, light yellow crystals (mp 45-46 °C, literature[5] mp 45 °C).

***(E)*-4-Phenyl-3-butenylamine.** In a three neck flask 3.97 g (100 mmol) of lithium aluminum hydride (LAH) in 260 ml of dry ether was stirred for 15 min under nitrogen atmosphere. To this suspension 12.1 g (69.1 mmol) of 1-phenyl-4-nitrobutadiene in 100 ml of dry ether was added dropwise. After the addition was completed, the resulting mixture was refluxed for 4 h, and then stirred at room temperature for 5 h. The reaction mixture was quenched with 4 ml of water, 4 ml of 15% NaOH, and 12 ml of water, and subsequently stirred for 30 min. The precipitate was filtered, washed with ethyl acetate, the combined filtrates were dried with anhydrous magnesium sulfate, and condensed *in vacuo* to afford 6 g of crude product (60%). Fractional distillation under reduced pressure afforded a colorless oil, bp 90-92 °C (3.5 mm), literature[5] bp 90-91 °C (3.5 mm). ^{1}H Nmr: 2.15-2.45 (2H, m br, $C\underline{H}_2N\underline{H}_2$), 2.60-2.92 (2H, br, $C{=}CC\underline{H}_2$), 5.85-6.59 (2H, m, Ph-$C\underline{H}{=}C\underline{H}$), 7.05-7.35 (5H, m, $C_6\underline{H}_5$).

General procedure for the preparation of the unsaturated amides: Most of the amides used for the cyclization reactions were derived from (*E*)-4-phenyl-3-butenylamine by acylation.

Method A (use of acid chlorides): 1 equivalent of the amine and 1.1 equivalents of triethylamine were stirred together in methylene chloride at 0-5 °C. To the mixture, 1.1 equivalents of an acid chloride in methylene chloride was added slowly. After the addition was over the reaction mixture was stirred for 30 min at room temperature, and then quenched with saturated $NaHCO_3$ solution. The organic layer was separated and washed twice with saturated $NaHCO_3$ solution and then with brine. The organic layer was dried with anhydrous $MgSO_4$ and condensed.

Method B (use of dicarboxylic acid anhydrides): 1 equivalent of the amine and 1.1 equivalents of an acid anhydride in benzene were refluxed for 3 h. The reaction mixture was then cooled to room temperature and extracted twice with 10% NaOH solution. The alkaline aqueous layer was cooled to 0 °C and made acidic with 10% HCl to precipitate the product. The precipitate was filtered, washed with cold ether, and dried overnight under reduced pressure. The acid was esterified by adding 1.2 equivalents of triethyloxonium tetrafluoroborate[10] to a stirring solution of the acid amide in methylene chloride. After stirring for 3 h, the reaction mixture was quenched with saturated $NaHCO_3$ solution. The organic layer was washed with saturated $NaHCO_3$ solution and then with brine. The organic layer was dried with anhydrous $MgSO_4$ and condensed *in vacuo*.

***N*-((*E*)-4-Phenylbut-3-enyl)-2-methylpropionamide, 2.** (*E*)-4-Phenyl-3-butenylamine (0.121 g, 0.82 mmol) was acylated with isobutyryl chloride (0.105 g, 0.98 mmol) via method A to afford 0.13 g of crude product (73%). Purification was by radial chromatography, eluting with 40% ethyl acetate in chloroform. An analytical sample was prepared by recrystallization from hexane. White crystals, mp 105-106 °C. ^{1}H Nmr: 1.14 (6H, d, J = 7.2, $C(C\underline{H}_3)_2$), 2.40 (2H, m, J = 6.8, $C{=}CC\underline{H}_2$, superimposed over $(CH_3)_2C\underline{H}$), 3.40 (2H, m, J = 6.2, $C\underline{H}_2N$), 5.85-6.25 (2H, m, Ph$C\underline{H}{=}C\underline{H}$), 7.15-7.43 (5H, m, $C_6\underline{H}_5$). Ir: 3330 (N-H), 1645 (C=O). ^{13}C Nmr 177.0 (NH-CO); 137.1, 132.2, 128.5, 127.2, 126.9, 125.0 ($\underline{C}_6H_5\underline{C}H{=}\underline{C}H$), 38.6 ($\underline{C}H_2N$), 35.5 ($C{=}\underline{C}CH_2$), 33.0 ($CO\underline{C}H$), 19.5 ($\underline{C}H_3)_2$. Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81. Found: C, 77.41; H, 8.83.

***N*-((*E*)-4-Phenylbut-3-enyl)-2,2-dimethylpropionamide, 3.** (*E*)-4-Phenyl-3-butenylamine (0.29 g, 1.97 mmol) was acylated with trimethylacetyl chloride (0.285 g, 2.4 mmol) via method A to afford 0.35 g of crude product (75%). Purification was done by radial chromatography, eluting with 40% ethyl acetate in chloroform. An

analytical sample was prepared by recrystallization from hexane. White crystals, mp 65 °C. ^{1}H Nmr: 1.10 (9H, s, $(C\underline{H}_3)_3$, 2.33 (2H, m, C=CC$\underline{H}_2$), 3.29 (2H, m, C$\underline{H}_2$N), 5.75-6.50 (2H, m, $C_6H_5C\underline{H}$=C$\underline{H}$), 7.10-7.30 (5H, m, $C_6\underline{H}_5$). Ir: 3390 (NH), 1645 (C=O). ^{13}C Nmr: 178.3 (NH$\underline{C}$O); 137.0, 132.1, 128.3, 127.0, 126.9, 125.9 ($\underline{C}_6H_5\underline{C}$H=$\underline{C}$H); 38.5 ($\underline{C}H_2$N), 38.4 (C=$\underline{C}CH_2$), 32.9 (CO$\underline{C}$), 27.4 ($\underline{C}H_3$)$_3$. Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15. Found: C, 77.87; H, 9.20.

***N*-((*E*)-4-Phenylbut-3-enyl)-3-carboethoxypropionamide, 4**, was prepared by acylation of (*E*)-4-phenyl-3-butenylamine (4.5 g, 31 mmol) with succinic anhydride (4.0 g, 40 mmol) and esterification by method B to afford 5.5 g of **4** (67%), which was purified by flash chromatography, eluting with 40% ethyl acetate in chloroform. An analytical sample was prepared by recrystallization from hexane. White crystals, mp 79 °C. ^{1}H Nmr: 1.22 (3H, t, J = 7.2, C$\underline{H}_3$), 2.24-2.73 (6H, m, C=C-C$\underline{H}_2$, CO-C$\underline{H}_2$C$\underline{H}_2$CO), 3.38 (2H, m, C$\underline{H}_2$N), 4.09 (2H, q, J = 7.2, OC$\underline{H}_2$CH$_3$), 5.85-6.50 (2H, m, PhC$\underline{H}$=C$\underline{H}$), 7.14-7.38 (5H, m, $C_6\underline{H}_5$). Ir: 3350 (NH) 1750 (ester C=O), 1655 (amide C=O). ^{13}C Nmr: 172.6 (NH-CO), 171.3 ($\underline{C}$OOEt); 136.9, 131.7, 128.2, 126.9, 125.8 ($\underline{C}_6H_5\underline{C}$H=$\underline{C}$H; one carbon buried), 60.3 (OCH$_2$), 38.8 (CH$_2$N), 32.7 (C=C$\underline{C}$H$_2$); 30.7, 30.6 (CO$\underline{C}$H$_2\underline{C}$H$_2$CO); 13.8 (CH$_3$). Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69. Found: C, 69.83; H, 7.70.

***N*-((*E*)-4-Phenylbut-3-enyl)-4-carboethoxybutyramide, 5**, was prepared by acylation of (*E*)-4-phenyl-3-butenylamine (0.5 g, 3.4 mmol) with glutaric anhydride (0.48 g, 4.2 mmol), followed by esterification via method B to afford 0.64 g of crude **5** (65%). Purification was done by flash chromatography, eluting with 40% ethyl acetate in chloroform. An analytical sample was prepared by recrystallization from hexane. White crystals, mp 64-65 °C. ^{1}H Nmr: 1.21 (3H, t, J = 7.0, C$\underline{H}_3$), 1.92-2.55 (8H, m, C=CC$\underline{H}_2$C, COC$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$CO), 3.39 (2H, m, C$\underline{H}_2$N), 4.08 (2H, q, J = 7.0, OC$\underline{H}_2$CH$_3$), 5.85-6.60 (2H, m, $C_6H_5C\underline{H}$=C$\underline{H}$), 7.10-7.38 (5H, m, $C_6\underline{H}_5$). Ir: 3310 (N-H), 1745 (C=O, ester), 1645 (C=O, amide). ^{13}C Nmr: 173.1 (C=O, amide), 172.2 (C=O, ester), 137.1, 132.3, 128.5, 127.2, 126.8, 126.0 ($\underline{C}_6H_5\underline{C}$H=$\underline{C}$H); 60.3 (O$\underline{C}H_2$), 38.7 ($\underline{C}H_2$N), 35.4 (C=C$\underline{C}H_2$); 33.2, 33.00 (CO$\underline{C}H_2CH_2\underline{C}H_2$CO), 20.9 (C$\underline{C}H_2$C), 14.1 (OCH$_2\underline{C}H_3$). Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01. Found: C, 70.47; H, 8.05.

***N*-((*E*)-4-Phenylbut-3-enyl)-3-benzyloxypropionamide, 7**, was prepared by acylating (*E*)-4-phenyl-3-butenylamine (0.245 g, 1.7 mmol) with 3-benzyloxypropionyl chloride[11] (0.33 g, 1.7 mmol) via method A to afford 0.44 g of crude product (85%). Purification by radial chromatography, eluting with 40% ethyl acetate in chloroform, and recrystallization from hexane yielded an analytical sample. White crystals, mp 78-79 °C. ^{1}H Nmr: 2.30-2.55 (4H, m, COC$\underline{H}_2$C, C=CC$\underline{H}_2$C), 3.35 (2H, m, C$\underline{H}_2$N), 3.70 (2H, t, J = 6.0, C$\underline{H}_2$OBn), 4.44 (2H, s, OC$\underline{H}_2C_6H_5$), 5.81-6.58 (2H, m, $C_6H_5C\underline{H}$=C$\underline{H}$), 7.10-7.37 (10H, m, C_6H_5). Ir: 3320 (N-H), 1640 (C=O, amide). ^{13}C Nmr: 171.5 (C=O); 137.6, 137.1, 132.0, 128.4, 127.6, 126.8, 125.9 ($\underline{C}_6H_5\underline{C}$H=$\underline{C}$H, $\underline{C}_6H_5CH_2$, three carbons buried); 73.1 ($C_6H_5\underline{C}H_2$), 66.3 ($\underline{C}$H$_2$OBn), 38.7 ($\underline{C}$H$_2$N), 37.0 (C=C$\underline{C}$H$_2$), 32.9 (CO$\underline{C}$H$_2$). Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49. Found: C, 77.55; H, 7.52.

***N*-((*E*)-4-Phenylbut-3-enyl)chloroacetamide, 8**, was prepared by acylation of (*E*)-4-phenyl-3-butenylamine (0.29 g, 1.36 mmol) with chloroacetyl chloride (0.15 g, 1.36 mmol) via method A to afford 0.26 g of crude

product (85%). Purification was done by radial chromatography, eluting with 40% ethyl acetate in hexane. An analytical sample was prepared by recrystallization from hexane. White crystals, mp 66-67 °C. ^{1}H Nmr: 2.46 (2H, m, C=CC$\underline{H}_2$), 3.46 (2H, m, C$\underline{H}_2$N), 4.02 (2H, s, COC$\underline{H}_2$Cl), 5.85-6.63 (2H, m, $C_6H_5C\underline{H}$=C$\underline{H}$), 7.15-7.40 (5H, m, $C_6\underline{H}_5$). Ir: 3360 (N-H), 1655 (C=O). Anal. Calcd for $C_{12}H_{14}ClNO$: C, 64.43; H, 6.31. Found: C, 64.32; H, 6.35.

***N*-((*E*)-4-Phenylbut-3-enyl)dichloroacetamide, 9**, was prepared by acylation of (*E*)-4-phenyl-3-butenylamine (0.245 g, 1.67 mmol) with dichloroacetyl chloride[12] (0.39 g, 2.0 mmol) via method A to afford 0.35 g of **9** (82%). Purification was accomplished using radial chromatography, eluting with 40% ethyl acetate in hexane. An analytical sample was prepared by recrystallization from hexane. White crystals, mp 93-94 °C. ^{1}H Nmr: 2.46 (2H, m, C=CC$\underline{H}_2$), 3.45 (2H, m, C$\underline{H}_2$N), 5.89 (1H, s, COC$\underline{H}$Cl$_2$), 5.85-6.62 (2H, m, $C_6H_5C\underline{H}$=C$\underline{H}$), 7.15-7.38 (5H, m, $C_6\underline{H}_5$). Ir: 3290 (NH), 1685 (C=O, amide). ^{13}C Nmr: 164.1 (C=O); 136.9, 133.1, 128.5, 127.4, 126.1, 125.7 ($\underline{C}_6H_5\underline{C}$H=$\underline{C}$H), 66.4 (CO$\underline{C}HCl_2$), 39.6 ($\underline{C}H_2$N), 32.4 (C=$\underline{C}CH_2$). Anal. Calcd for $C_{12}H_{13}Cl_2NO$: C, 55.83; H, 5.08. Found C, 55.99; H, 5.11.

***N*-((*E*)-4-Phenylbut-3-enyl)-3-chloropropionamide, 10** was prepared by acylation of (*E*)-4-phenyl-3-butenylamine (0.23 g, 1.6 mmol) with 3-chloropropionyl chloride (0.2 g, 1.6 mmol) via method A to afford 0.296 g of product (78%). Purification was done by radial chromatography, eluting with 40% ethyl acetate in chloroform. An analytical sample was prepared by recrystallization from hexane. White crystals, mp 97-100 °C, literature[5] mp 95.5-100 °C (recrystallization from alcohol). ^{1}H Nmr: 2.27-2.67 (4H, m, C=CC$\underline{H}_2$, COC$\underline{H}_2$), 3.28-3.89 (4H, m, C$\underline{H}_2$Cl, C$\underline{H}_2$N), 5.85-6.62 (2H, m, $C_6H_5C\underline{H}$=C$\underline{H}$), 7.16-7.39 (5H, m, $C_6\underline{H}_5$).

***N*-((*E*)-4-Phenylbut-3-enyl)-2,3-dicarboethoxypropionamide, 15**. To 3.0 mmol of LDA (2.0 ml of 1.6 M n-butyllithium and 0.3 g of diisopropylamine at 0 °C) in 10 ml of dry THF, was added 0.5 g of diethyl succinate (2.9 mmol) in 5 ml of dry THF at -78 °C and stirred for 30 min. Then to the reaction mixture dry CO_2 was added (either by bubbling through or as a solid) and slowly warmed to room temperature. The reaction mixture was then quenched with 20 ml of brine and washed with ether. The ether extract was discarded and the aqueous layer was acidified with 10% HCl solution at 0 °C. The acidic aqueous layer was extracted with ethyl acetate, dried with anhydrous $MgSO_4$, and condensed in vacuo to afford 0.5 g of 2,3-dicarboethoxypropionic acid, which was used without further purification. The acid was transformed into its acid chloride by heating with thionyl chloride (5ml) at 60 °C. (*E*)-4-phenyl-3-butenylamine (0.1 g, 0.68 mmol) was acylated with 0.23 g of the acid chloride (0.68 mmol) via method A to afford 0.165 g of **15** (60%). Purification was accomplished by radial chromatography, eluting with 40% ethyl acetate in hexane. ^{1}H Nmr: 1.05-1.33 (6H, 2t, J = 7.0, OCH$_2$C$\underline{H}_3$), 2.25-2.55 (2H, m, C=CC$\underline{H}_2$), 2.92 (2H, d, J = 7.8, CHC$\underline{H}_2$CO$_2$Et), 3.23-3.75 (3H, m, C$\underline{H}_2$N, COC$\underline{H}$CO), 4.09 (4H, 2q, J = 7.0, OC$\underline{H}_2$CH$_3$), 5.84-6.60 (2H, m, $C_6H_5C\underline{H}$=C$\underline{H}$), 7.12-7.36 (5H, m, $C_6\underline{H}_5$). Ir: 3345 (N-H), 1740 (C=O, ester), 1660 (C=O, amide). ^{13}C Nmr: 171.5 (C=O, amide); 169.7, 166.7 (C=O, ester); 137.1, 132.4, 128.4, 127.2, 126.5, 126.0, ($\underline{C}_6H_5\underline{C}$H=$\underline{C}$H); 61.8, 60.8 (O$\underline{C}H_2CH_3$), 48.2 (CO$\underline{C}$HCO), 39.2 ($\underline{C}H_2$N), 32.7 ($\underline{C}H_2$N and $\underline{C}$H$_2$CO superimposed), 13.9 ($\underline{C}$H$_3$).

***N*-((*E*)-4-Phenylbut-3-enyl)-carbomethoxyacetamide, 16**, was prepared by acylating (*E*)-4-phenyl-3-butenyl amine (0.19 g, 1.3 mmol) with the half ester/half acid chloride of malonic acid[13] (0.213 g, 1.56 mmol) via method A to afford 0.225 g of **16** (70%). Purification was achieved using radial chromatography, eluting with 40% ethyl acetate in chloroform. ^{1}H Nmr: 2.43 (2H, m, C=CC$\underline{H}_2$), 3.28-3.57 (4H, m, COC$\underline{H}_2$CO, C-C$\underline{H}_2$-N), 3.66 (3H, s, OC$\underline{H}_3$), 5.82-6.56 (2H, m, $C_6H_5C\underline{H}$=C$\underline{H}$), 7.12-7.47 (5H, m, $C_6\underline{H}_5$). ^{13}C Nmr 169.3 (C=O, amide), 164.9 (C=O, ester); 137.0, 132.1, 128.3, 127.0, 126.5, 125.9 ($\underline{C}_6H_5\underline{C}$H=$\underline{C}$H); 52.1 (O$\underline{C}H_3$); 41.1, 38.9 (CO$\underline{C}H_2$CO, $\underline{C}H_2$N); 32.6 (C=C$\underline{C}H_2$).

***N*-((*E*)-4-Phenylbut-3-enyl)-2-carbomethoxy-2-methylpropionamide, 17**. To 0.35 mmol of LDA (0.22 ml of 1.6M *n*-butyllithium and 0.035 g of diisopropylamine at 0 °C) in 1 ml of dry THF, was added 0.073 g of **16** (0.3 mmol) in 0.5 ml of dry THF at -78 °C and stirred for 20 min. The reaction mixture was then quenched with 0.056 ml of methyl iodide (0.9 mmol) at -78 °C and slowly warmed to room temperature. The reaction mixture was quenched with brine and extracted with ethyl acetate. The separated organic layer was dried with anhydrous $MgSO_4$ and condensed *in vacuo*. Purification by radial chromatography, eluting with 40% ethyl acetate in hexane, afforded 0.055 g of **17** (67%). ^{1}H Nmr: 1.42 (6H, s, $(C\underline{H}_3)_2$), 2.41 (2H, m, C=CC$\underline{H}_2$), 3.41 (2H, m, C$\underline{H}_2$N), 3.62 (3H, s, OC$\underline{H}_3$), 5.84-6.60 (2H, m, $C_6H_5C\underline{H}$=C$\underline{H}$), 7.15-7.38 (5H, m, $C_6\underline{H}_5$). Ir: 3360 (NH), 1735 (C=O, ester), 1655 (C=O, amide). ^{13}C Nmr: 175.3 (C=O, amide), 171.6 (C=O, ester); 137.0, 132.4, 128.4, 127.2, 126.7, 126.0 ($\underline{C}_6H_5\underline{C}$H=$\underline{C}$H); 52.5 (O$\underline{C}H_3$), 49.8 (CO$\underline{C}(CH_3)_2$CO), 39.0 ($\underline{C}H_2$N), 32.8 (C=CCH$_2$C), 23.6 ($\underline{C}H_3)_2$. Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69. Found: C, 69.74; H, 7.72.

General procedure for cyclization reactions of unsaturated amides using trimethylsilyl-polyphosphate (PPSE).

Method C: A mixture of 1.5 g of P_2O_5, 3 ml of hexamethyldisiloxane, and 7 ml of CCl_4 was refluxed for 1.5 h. The resulting colorless solution of PPSE was cooled to room temperature and added to 1 mmol of an amide. The reaction mixture was refluxed for 3 to 7 h and cooled. Generally a successful cyclization was indicated by a gummy precipitate on the walls of the flask. *Note: the product is in this precipitate.* The reaction mixture was quenched with 5 ml of water and transferred to a separatory funnel. The gummy precipitate was dissolved in two successive 5 ml portions of water, and added to the contents of the separatory funnel. The layers were separated and the organic layer was washed with 5 ml of 10% HCl. The combined aqueous layers were cooled to 0 °C and brought to pH 9 with 50% NaOH solution. The aqueous phase was then extracted thrice with 10 ml of chloroform. The chloroform extracts were combined, dried with magnesium sulfate, and condensed *in vacuo*.

3-Benzylidene-2-methyl-Δ^1-pyrroline, 12a. The amide **1** (0.203 g, 1.0 mmol) was refluxed for 3 h with PPSE (1.5 g P_2O_5, 3 ml of hexamethyldisiloxane, and 7 ml of CCl_4) via method C to afford 0.15 g of **12a** (88%). Purification was achieved using radial chromatography, eluting with 40% ethyl acetate in chloroform. The spectroscopic properties were identical with those reported earlier.[2c]

3-Benzylidene-2-isopropyl-Δ^1-pyrroline. *N*-((*E*)-4-Phenylbut-3-enyl)-2-methylpropionamide (0.082 g, 0.38 mmol) was refluxed for 3 h with PPSE (0.6 g P_2O_5, 1.1 ml of hexamethyldisiloxane, 2.6 ml of CCl_4) via

method C to afford 0.07 g of product, (90%) which was purified by radial chromatography, eluting with 40% ethyl acetate in chloroform. An analytical sample was prepared by Kugelrohr distillation, bp 70-75 °C (0.5 mm). ^{1}H Nmr: 1.27 (6H, d, J = 6.6, $(C\underline{H}_3)_2$), 2.70-3.10 (3H, m, br, C=CC$\underline{H}_2$, N=CC$\underline{H}$), 3.90-4.10 (2H, m, br, C$\underline{H}_2$N), 6.73 (1H, t, J = 2.9, $C_6H_5C\underline{H}$), 7.28-7.48 (5H, m, $C_6\underline{H}_5$). Ir: 1610 (C=N). ^{13}C Nmr: 179.5 (C=N); 141.1, 136.6, 128.3, 128.0, 127.1, 123.4 ($\underline{C}_6H_5\underline{C}H=\underline{C}$); 58.3 ($\underline{C}H_2N$), 29.8 (C=C$\underline{C}H_2$), 27.2 (N=C$\underline{C}$H), 20.5 $(\underline{C}H_3)_2$. HRMS Calcd for $C_{14}H_{17}N$: M^+= 199.1361. Found M^+= 199.1334.

3-Benzylidene-2-*tert*-butyl-Δ^1-pyrroline. *N-((E)*-4-Phenylbut-3-enyl)-2,2-dimethylpropionamide (0.189 g, 0.78 mmol) was refluxed for 3 h with PPSE (1.5 g P_2O_5, 3 ml of hexamethyldisiloxane, 7 ml of CCl_4) via method C to afford 0.138 g of product (81%), which was purified by radial chromatography, eluting with 40% ethyl acetate in chloroform. An analytical sample was prepared by Kugelrohr distillation, bp 100-110 °C (2 mm). ^{1}H Nmr: 1.14 (9H, s, $(C\underline{H}_3)_3$, 2.75-2.98 (2H, m, C=CC$\underline{H}_2$), 3.35-4.03 (2H, m, C$\underline{H}_2$N), 7.02 (1H, t, J = 2.9, $C_6H_5C\underline{H}$), 7.22-7.45 ($C_6\underline{H}_5$). Ir 1615 (C=N). ^{13}C Nmr: 180.6 (C=N); 140.7, 137.1, 128.6, 128.3, 127.3, 126.3 ($\underline{C}_6H_5\underline{C}H=\underline{C}$); 57.6 ($\underline{C}H_2N$), 35.8 (C=C$\underline{C}H_2$), 31.40 (N=C$\underline{C}(CH_3)_3$), 29.2 $(\underline{C}H_3)_3$. Anal. Calcd for $C_{15}H_{19}N$: C, 84.46; H, 8.98. Found: C, 84.38; H, 9.00.

3-Benzylidene-2-(2-carboethoxyethyl)-Δ^1-pyrroline, 12b. The amide **4** (0.89 g, 2.9 mmol) was refluxed for 5 h with PPSE (6.7 g P_2O_5, 13.5 ml of hexamethyldisiloxane, 31 ml of CCl_4) via method C to afford 0.45 g of **12b** (60%). Purification was done by radial chromatography, eluting with 40% ethyl acetate in chloroform. An analytical sample was prepared by Kugelrohr distillation, bp 120-130 °C (2 mm). ^{1}H Nmr: 1.27 (3H, t, J = 7.2, $OCH_2C\underline{H}_3$), 2.79-2.93 (6H, m, N=CC$\underline{H}_2$C$\underline{H}_2$CO, C=CC$\underline{H}_2$), 4.0-4.05 (2H, m, C$\underline{H}_2$N), 4.17 (2H, q, J = 7.2, $OC\underline{H}_2CH_3$), 6.78 (1H, t, J = 2.78, $C_6H_5C\underline{H}$), 7.26-7.48 (5H, m, $C_6\underline{H}_5$). Ir: 1750 (C=O), 1620 (C=N). ^{13}C Nmr: 173.7, 173.1 (C=O, C=N); 142.0, 136.7, 128.7, 128.4, 127.6, 124. ($\underline{C}_6H_5\underline{C}H=\underline{C}$); 60.3 ($OCH_2$), 58.8 ($CH_2N$); 30.5, 29.9 (C=C$\underline{C}H_2$, N=C$\underline{C}H_2$); 24.4 ($\underline{C}H_2CO$), 14.0 ($OCH_2\underline{C}H_3$). Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44. Found: C, 73.99; H, 7.48.

3-Benzylidene-2-(3-carboethoxypropyl)-Δ^1-pyrroline, 12c. The amide **5** (0.465 g, 1.6 mmol) was refluxed for 5 h with *PPSE (2.49 g P_2O_5, 4.8 ml of hexamethyldisiloxane, 11.0 ml of CCl_4) via method C to* afford 0.25 g of **12c** (60%). Purification by radial chromatography, eluting with 40% ethyl acetate in chloroform., and Kugelrohr distillation afforded an analytical sample, bp 120-130 °C (2 mm). ^{1}H Nmr: 1.12 (3H, t, J = 7.0, $OCH_2C\underline{H}_3$), 1.80-2.76 (8H, m, C=CC$\underline{H}_2$, N=CC$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$CO), 3.75-4.14 (4H, m, C$\underline{H}_2$N, OC$\underline{H}_2$), 6.52-6.61 (1H, t, J = 2.8, $C_6H_5C\underline{H}$), 7.05-7.31 (5H, m, $C_6\underline{H}_5$). Ir: 1740 (C=O), 1610 (C=N). ^{13}C Nmr: 173.9, 172.4 (C=O, C=N); 141.5, 136.2, 128.1, 127.8, 127.0, 123.4 ($\underline{C}_6H_5\underline{C}H=\underline{C}$); 59.4 ($OCH_2$), 58.3 ($CH_2N$), 33.1 (C=C$CH_2$); 29.2, 27.9 (N=C$\underline{C}H_2$, $\underline{C}H_2CO$); 21.2 ($CH_2\underline{C}H_2CH_2$), 13.6 ($OCH_2\underline{C}H_3$). Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.23; H, 7.81; N, 5.16. Found: C, 75.14; H, 7.84; N, 5.12.

3-Benzylidene-2-chloromethyl-Δ^1-pyrroline. *N-((E)*-4-Phenylbut-3-enyl)-chloroacetamide, **8**, (0.19 g, 0.45 mmol) was refluxed for 7 h with PPSE (0.75 g P_2O_5, 1.5 ml of hexamethyldisiloxane, 4 ml of CCl_4) via method C to afford 0.057 g of the product (62%). Purification was accomplished by radial chromatography, eluting

with 40% ethyl acetate in hexane. An analytical sample was prepared by recrystallization from hexane. ^{1}H Nmr: 2.84-3.07 (2H, m, br, C=CC$\underline{H}_2$), 4.01-4.21 (2H, m, br, C$\underline{H}_2$N), 4.48 (2H, s, N=CC$\underline{H}_2$Cl), 6.86 (1H, t, J = 3.0, $C_6H_5C\underline{H}$), 7.23-7.51 (5H, m, $C_6\underline{H}_5$). Ir: 1605 (C=N). Anal. Calcd for $C_{12}H_{12}ClN$: C, 70.07; H, 5.88. Found: C, 70.08; H, 5.90.

General procedure for asymmetric reduction of the cyclized products.

Method D: a solution of Z-Pro (4.5 mmol) in 10 ml of THF was added, with cooling, to a stirred suspension of $NaBH_4$ (1.5 mmol) in 3 ml of THF. The mixture was stirred at room temperature for 2 h and then a solution of a cyclic imine (1.15 mmol) in 10 ml of THF was added at –30 °C. The reaction mixture was then stirred for 12 h at –30 °C. The reaction mixture was quenched with 5% HCl solution, heated at 60-70 °C for 30 min, and condensed. The aqueous residue was made alkaline with potassium carbonate and extracted with ethyl acetate. The ethyl acetate extracts were washed with 20% potassium carbonate solution, dried with magnesium sulfate, and condensed.

3-Benzylidene-2-methylpyrrolidine, 13a. The pyrroline **12a** (0.1 g, 0.6 mmol) was reduced with NaBH(Z-Pro)$_3$. (0.045 g, 1.2 mmol of $NaBH_4$ and 0.9 g, 3.6 mmol of Z-Pro) via method D to afford 0.097 g of **13a** (95%). ^{1}H Nmr: 1.78 (3H, d, *J* = 6.0, C$\underline{H}_3$), 2.68-3.88 (5H, m, C=CC$\underline{H}_2$, C$\underline{H}_2$N, C=CC$\underline{H}$N), 6.18-6.28 (1H, m, $C_6H_5C\underline{H}$), 7.17-7.36 (5H, m, $C_6\underline{H}_5$). ^{13}C Nmr: 147.9, 138.2, 128.2, 127.9, 126.1, 119.9 ($\underline{C}_6H_5C\underline{H}$=$\underline{C}$), 59.0 (C=$\underline{C}$CHN), 46.0 ($\underline{C}H_2$-N), 32.3 (C=$\underline{C}CH_2$), 20.20 ($CH_3$). Dry HCl gas was bubbled through an ethereal solution of crude **13a** for 5 min at 0 °C to afford the HCl salt, which was recrystallized from methanol–ether to obtain light brown crystals, mp 203-204 °C. Anal. Calcd for $C_{12}H_{16}ClN$: C, 68.73; H, 7.69. Found: C, 68.62; H, 7.72. Pirkle analysis[9] showed the major enantiomer to be *S*, present in 50% enantiomeric excess.

1-Aza-6-benzylidenebicyclo[3.3.0]octan-2-one, 14a. The pyrroline ester **12b** (0.2 g, 0.78 mmol) was reduced with NaBH(Z-Pro)$_3$ (0.6 g, 1.56 mmol of $NaBH_4$ and 1.16 g, 4.7 mmol Z-Pro) via method D to afford 0.129 g of (–) **14a** (78%) ($[\alpha]_D^{25°}$ –39°, EtOH). Purification was accomplished by radial chromatography, eluting with 40% ethyl acetate in chloroform. An analytical sample was prepared by recrystallization from hexane. White coral-like crystals, mp 107-109 °C. ^{1}H Nmr: 1.80-3.30 (6H, m, C$\underline{H}_2$C$\underline{H}_2$CO, C=CC$\underline{H}_2$), 3.85-4.20 (2H, m, C$\underline{H}_2$N), 4.40-4.65 (1H, m, br, C=CC$\underline{H}$N), 6.21-6.40 (1H, m, br, C_6H_5CH), 7.15-7.40 (5H, m, $C_6\underline{H}_5$). Ir: 1675 (C=O). ^{13}C Nmr: 175.3 (C=O); 142.6, 136.8, 128.3, 128.1, 126.8, 122.0 ($\underline{C}_6H_5C\underline{H}$=$\underline{C}$), 64.75 (C=$\underline{C}$CHN), 41.45 ($\underline{C}H_2$N), 33.75 (C=$\underline{C}CH_2$), 31.54 ($\underline{C}H_2$CO), 27.75 ($\underline{C}H_2$). Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09. Found: C, 78.75; H, 7.11.

1-Aza-7-benzylidenebicyclo[4.3.0]nonan-2-one, 14b. The pyrroline ester **12c** (0.045 g, 0.74 mmol) was reduced with NaBH(Z-Pro)$_3$ (0.06 g, 1.5 mmol of $NaBH_4$ and 1.12 g, 4.5 mmol of Z-Pro) via method D to afford 0.129 g of (–) **14b** (77%) ($[\alpha]_D^{25°}$ –40°, EtOH). Purification was achieved by radial chromatography, eluting with 40% ethyl acetate in chloroform. An analytical sample was prepared by recrystallization from hexane. White coral-like crystals, mp 80-83 °C. ^{1}H Nmr: 1.95-3.55 (8H, m, br, C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$CO, C=CC$\underline{H}_2$), 3.98-4.40 (3H, m, br, C=CC$\underline{H}_2$N, C$\underline{H}$N), 6.27-6.38 (1H, m, $C_6H_5C\underline{H}$=C), 7.18-7.40 (5H, m, $C_6\underline{H}_5$). Ir: 1640 (C=O). ^{13}C Nmr:

167.8 (C=O); 142.0, 136.4, 127.8, 126.3, 120.8 ($\underline{C}_6H_5\underline{C}H=\underline{C}$), 61.0 (C=C$\underline{C}$HN), 43.0 ($\underline{C}H_2N$), 30.6 (C=C$\underline{C}H_2$); 27.7, 27.5, 20.2. HRMS Calcd for $C_{15}H_{17}NO$: M^+=227.1310. Found: M^+=227.1295.

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