Transition Metal-Catalyzed Radical Cyclizations: A Low-Temperature Process for the Cyclization of N-Protected *N*-Allyltrichloroacetamides to Trichlorinated γ-Lactams and Application to the Stereoselective Preparation of β,γ-Disubstituted γ-Lactams

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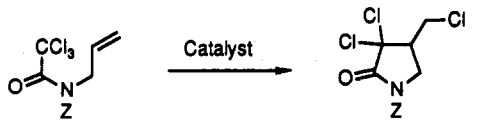
Cyclizations of N-substituted *N*-allyltrichloroacetamides, where the substituent is an alkyl, Cbz, Boc, Ts, or Ms group, are catalyzed by a 1:1 mixture of CuCl and bipyridine to give the corresponding β,γ-trichlorinated γ-lactams in high yields. The reactions proceed at temperatures from −78 °C to room temperature. Cyclizations of *N*-allyltrichloroacetamides of acyclic secondary allylic amines are achieved with good selectivity; the cis/trans ratios of the γ-lactams formed were dependent on the substituents on the nitrogen atom. The stereochemical outcome is compared with that of free-radical cyclization.

Introduction

Transition metal-catalyzed radical cyclizations have received considerable attention from organic chemists.[1] In our previous papers, we reported copper- and ruthenium-catalyzed processes for the preparation of α,α,γ-trichlorinated γ-lactones[2] and lactams[3,4] from allyl trichloroacetates and *N*-allyltrichloroacetamides, respectively. Weinreb has reported similar approaches that provide novel methods for the preparation of polychlorinated cyclopentanes or hexanes from ω-polyhaloalkenes.[5] It is important from a synthetic viewpoint that the procedures are simple and the products are generally isolated in high yields. However, it should be noted that a general disadvantage of these catalytic processes is that the reactions require high temperatures (>140 °C).

In this context, we have been interested in the development of transition metal-catalyzed radical cyclizations that proceed at lower temperatures. In this paper, we report that the cyclization of *N*-allyltrichloroacetamides below room temperature can be achieved by the judicious choice of the catalyst and the protecting group on the amide nitrogen. As shown in Scheme I, N-allyltrichloroacetamides having a methyl, allyl, benzyl, tosyl, mesyl, t-Boc, or Cbz group on the amide nitrogen undergo the cyclization at −78 °C to room temperature catalyzed by a 1:1 mixture of CuCl and bipyridine to give the corresponding N-substituted trichlorinated γ-lactams in high yields. Application of the low-temperature cyclization to the preparation of β,γ-disubstituted γ-lactams from acyclic trichloroacetamides of secondary allylic amines provides a stereoselective route to cis- and trans-β,γ-disubstituted γ-lactams from acyclic precursors.[6]

Scheme I



1a	[Z = H]	**2a**	[Z = H]
1b	[Z = $CH_2CH{=}CH_2$]	**2b**	[Z = $CH_2CH{=}CH_2$]
1c	[Z = CH_2Ph]	**2c**	[Z = CH_2Ph]
1d	[Z = Ts]	**2d**	[Z = Ts]
1e	[Z = Cbz]	**2e**	[Z = Cbz]

Results and Discussion

Cyclization of N-Substituted *N*-Allyltrichloroacetamides. As reported in our previous paper, cyclizations of *N*-allyltrichloroacetamides without nitrogen substituents were catalyzed by $RuCl_2(PPh_3)_3$ in benzene or toluene at 140 °C.[3a] Similar reactions of *N*-alkyl-*N*-allyltrichloroacetamides proceeded at 80–110 °C. In the latter reactions, CuCl in acetonitrile was also an effective catalyst. Further studies on the cyclizations of other N-substituted *N*-allyltrichloroacetamides demonstrated to us that the substrates with electron-withdrawing substituents such as Cbz and tosyl groups underwent the cyclization at temperatures lower than 80 °C. In Table I, entries 1–7, are shown the optimized results of the cyclization of N-substituted *N*-allyltrichloroacetamides **1b–1e** with $RuCl_2(PPh_3)_3$ or CuCl as the catalyst. In the extreme case, the reaction of **1d** with 30 mol % of CuCl yielded **2d** at room temperature. Compound **1a** did not react below 100 °C with either of the catalysts. Thus, the substituents of the amide function are important for the low-temperature cyclization; the rate increased in the order **1b, 1c < 1e < 1d**.

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0022-3263/93/1958-0464$04.00/0

Table I. Effect of Catalysts on the Cyclizations of *N*-Allyltrichloroacetamide Derivatives[a]

entry	substrate	catalyst (%)	temp (°C)	time (h)	product	yield (%)
1	**1b**	Ru (5)	140	1	**2b**	84
2	**1b**	Cu (30)	80	20	**2b**	81
3	**1c**	Ru (5)	110	1	**2c**	90
4	**1c**	Cu (30)	80	18	**2c**	68
5	**1d**	Ru (5)	50	8	**2d**	35
6	**1d**	Cu (30)	rt	24	**2d**	97
7	**1e**	Cu (30)	80	4	**2e**	80
8	**1b**	Cu* (30)	rt	2	**2b**	98
9	**1c**	Cu* (30)	rt	1	**2c**	98
10	**1c**	Cu* (30)	−78	62	**2c**	46
11	**1d**	Cu* (5)	rt	0.2	**2d**	91
12	**1d**	Cu* (5)	−78	141	**2d**	98
13	**1e**	Cu* (30)	rt	2	**2e**	78
14	**1e**	Cu* (30)	−78	108	**2e**	70

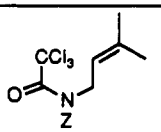
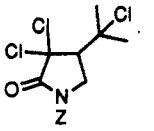
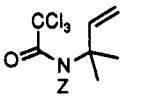
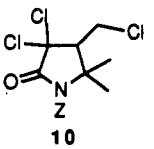
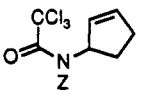
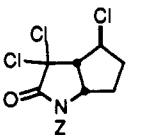
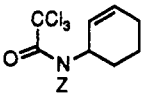
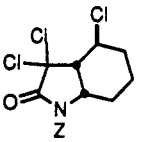
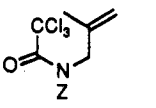
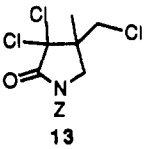
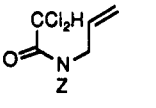
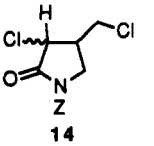
[a] Ru = $RuCl_2(PPh_3)_3$ in benzene. Cu = CuCl in acetonitrile. Cu* = CuCl/bipy in CH_2Cl_2. Detailed data are given in Table Sup-I and Sup-II in the supplementary material.

Screening of the catalyst in the cyclization of **1b–1e** resulted in the discovery that a 1:1 mixture of CuCl and bipyridine in CH_2Cl_2 catalyzed the cyclization more rapidly than did CuCl alone in acetonitrile or $RuCl_2(PPh_3)_3$ in benzene. As shown in Table I, entries 8–14, the use of the CuCl/bipyridine catalyst resulted in the formation of the corresponding lactams **2b–2e** at −78 °C to room temperature. The cyclization of **1a** did not occur under these conditions. Bidentate tertiary amines such as TMEDA and sparteine were also effective as ligands of CuCl, but no reaction occurred with CuCl in the presence of ethylenediamine, *N,N'*-dimethylethylenediamine, pyridine, *N,N*-dimethylbenzylamine, or phosphines. Use of THF or dichloroethane as the solvent also gave rates comparable to those in dichloromethane, whereas the reaction in acetonitrile was slower.

In Table II are shown the results of the cyclizations of several *N*-benzyl-*N*-allyltrichloroacetamides with the copper–amine catalyst. With 30 mol % of the catalyst, the reactions were complete within 3 h at room temperature as shown in entries 1–5. The single diastereomers shown in the table were obtained in the cyclizations of *N*-(2-cyclopentenyl) and *N*-(2-cyclohexenyl) analogues **5** and **6**. The cyclization of *N*-methallyl analogue **7** produced a quaternary carbon. The cyclization of *N*-allyl-*N*-benzyldichloroacetamide was not achieved with either $RuCl_2(PPh_3)_3$ in benzene or CuCl in acetonitrile but occurred slowly at room temperature with the CuCl/bipyridine catalyst. The reaction was completed by heating the reaction mixture in dichloroethane at 80 °C for 3 h. Attempted cyclization of *N*-allyl-*N*-benzyliodoacetamide failed even at 80 °C.

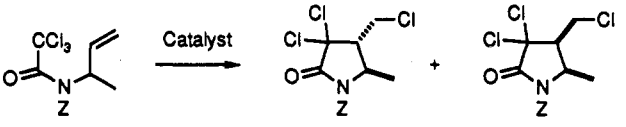
Stereoselective Cyclization of *N*-Allyltrichloroacetamides of Acyclic Secondary Allylic Amines. Cyclizations of N-substituted *N*-(1-buten-3-yl)trichloroacetamides **15b–15g** with the CuCl/bipyridine catalyst also proceeded smoothly below room temperature. As reported previously, *N*-(1-buten-3-yl)trichloroacetamide (**15a**) was subjected to the ruthenium-catalyzed cyclization of 140 °C to give trans-lactam **16a** as the major stereoisomer (trans:cis = 88:12).[3c] In contrast, the stereoselectivities observed in the cyclizations of **15b–15g** were dependent on the protecting group, and in several cases, the cis isomer was formed with good selectivity as shown in Table III. Cyclization of either the *N*-benzyl- or *N*-methyl-*N*-allyltrichloroacetamide **15b** or **15c** afforded the corresponding trans isomer predominantly (trans:cis = 7:3–9:1). In contrast, the cyclization of the of *N*-tosyl, mesyl, Cbz, or t-Boc analogue **15d–15g** provided the corresponding cis isomer with good stereoselectivity (trans:cis = 2:8–1:9). The stereoselectivity was nearly independent of the catalyst used, whereas higher selectivity was achieved at lower temperature. The low-temperature process with the CuCl/bipyridine catalyst provided a synthetic route to *cis*-4,5-dimethyl-2-pyrrolidinone derivatives, from which

Table II. Cyclizations of *N*-Benzyl-*N*-allyltrichloroacetamides by CuCl/bipy Catalyst (Z = CH_2Ph)

entry	substrate	temp (°C)	time (h)	product	yield (%)
1	 **3**	r.t.	1.5	 **9**	98
2	 **4**	r.t.	1	 **10**	96
3	 **5**	r.t.	1	 **11**	61
4	 **6**	r.t.	1.5	 **12**	98
5	 **7**	r.t.	1	 **13**	64
6	 **8**	r.t. 80	13 4	 **14**	59 98[a]

[a] The reaction was carried out in dichloroethane.

Scheme II



15a [Z = H]
15b [Z = CH_2Ph]
15c [Z = Me]
15d [Z = Ts]
15e [Z = Ms]
15f [Z = Cbz]
15g [Z = t-Boc]

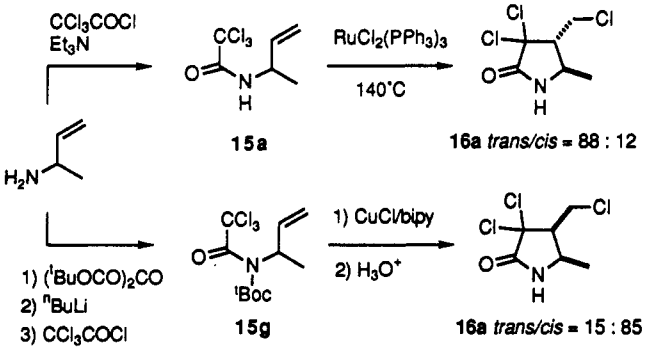
16a [Z = H]
16b [Z = CH_2Ph]
16c [Z = Me]
16d [Z = Ts]
16e [Z = Ms]
16f [Z = Cbz]
16g [Z = t-Boc]

Table III. Cyclizations of *N*-(1-Buten-3-yl)trichloroacetamide Derivatives[a]

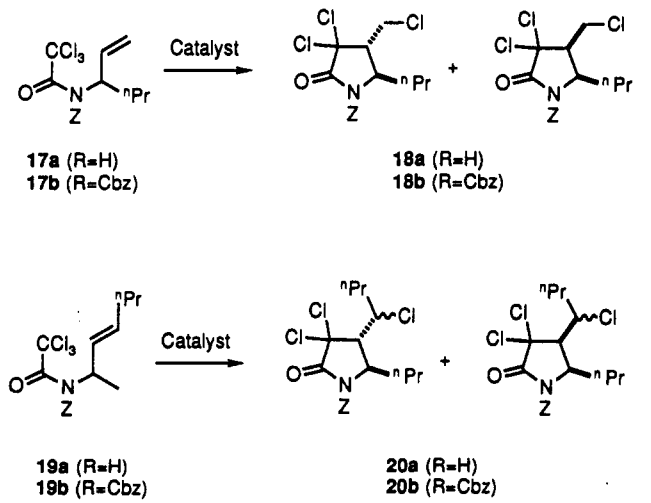
substrate	catalyst (%)	temp (°C)	time (h)	product	yield (%)	ratio (trans/cis)
15b	Ru (5)	140	6	**16b**	86	71/29
15b	Ru (5)	110	24	**16b**	53	76/24
15b	Cu (30)	110	13	**16b**	84	78/22
15b	Cu (30)	80	35	**16b**	72	86/14
15b	Cu* (30)	rt	2	**16b**	98	88/12
15b	Cu* (30)	−15	43	**16b**	93	95/5
15c	Cu* (30)	−15	1	**16c**	98	90/10
15d	Cu* (5)	rt	0.1	**16d**	74	22/78
15d	Cu* (5)	−15	24	**16d**	90	15/85
15d	Cu* (5)	−78	72	**16d**	98	10/90
15e	Cu* (30)	rt	1	**16e**	98	28/72
15e	Cu* (30)	−15	1	**16e**	98	20/80
15e	Cu* (30)	−78	78	**16e**	98	13/87
15f	Cu* (30)	rt	2	**16f**	88	23/77
15f	Cu* (30)	−15	25	**16f**	76	20/80
15f	Cu* (30)	−70	86	**16f**	83	14/86
15g	Cu* (30)	rt	1.5	**16g**	98	23/77
15g	Cu* (30)	−15	23	**16g**	80	14/86

[a] Ru = $RuCl_2(PPh_3)_3$ in benzene. Cu = CuCl in acetonitrile. Cu* = CuCl + bipyridine in dichloromethane. Detailed data are given in Table Sup-III in the supplementary material.

Scheme III



Scheme IV



the substituent on the lactam can be easily removed. Thus, the stereoselective synthesis of the trans and cis isomers of **16a** from 3-amino-1-butene was achieved as illustrated in Scheme III.

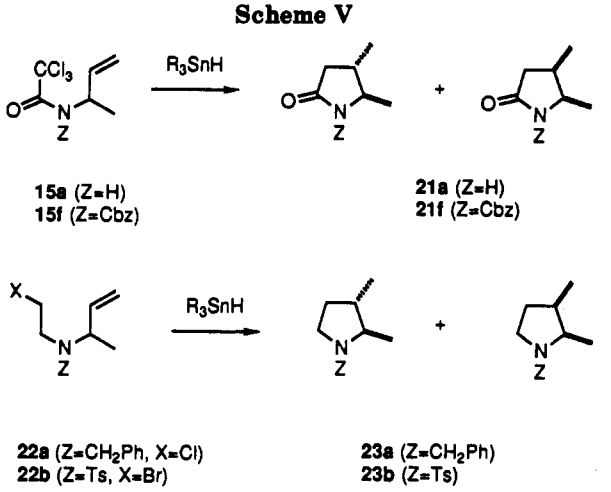
The diastereoselectivities in the cyclizations of other *N*-allyltrichloroacetamides were also dependent on the nitrogen substituents as shown in Scheme IV and Table IV. Cyclizations of **17a** and **19a** with a catalytic amount of $RuCl_2(PPh_3)_3$ at 140 °C afforded the corresponding trans isomers. Good cis-selectivity (trans:cis = 20:80) was observed in the cyclization of **19b** with the CuCl/bipyridine

Table IV. Stereoselective Cyclizations of 17 and 19

substrate	catalyst[a] (mol %)	temp (°C)	time (h)	product	yield (%)	ratio (trans/cis)
17a	Ru (5)	140	2	**18a**	83	89:11[b]
17b	Cu (100)	50	2	**18b**	78	74:26
17b	Cu* (30)	rt	2	**18b**	56	61:39
19a	Ru (5)	140	1	**20a**	84	88:12[b,c]
19b	Cu (100)	50	29	**20b**	83	36:64[c]
19b	Cu* (30)	−15	23	**20b**	98	20:80[c]

[a] Ru = $RuCl_2(PPh_3)_3$, Cu = CuCl/MeCN, Cu* = CuCl/bipy. [b] The ratios were determined after reductive dechlorination. [c] Reference 3c.

Scheme V



catalyst at −15 °C. In contrast, the cyclization of **17b** with the CuCl/bipyridine catalyst at room temperature afforded a mixture of isomers (trans:cis = ca. 6:4). Thus, introduction of the Cbz group on the amide function and lower reaction temperatures generally contribute to an increase in the cis isomer in the cyclizations of **15f**, **17b**, and **19b**; however, the cis/trans ratio was dependent on the structure of the substrates.

Comparison of the Cu(I)-Catalyzed Cyclization with the Tin-Mediated Radical Cyclization. It is known that pyrrolidine or pyrrolidinone derivatives can be prepared by tin-mediated radical cyclizations of certain unsaturated amides[7] and amines.[8] Nevertheless, nothing has been reported about the effect of nitrogen substituents on the stereoselectivity of the reaction. Treatment of **15a** and **15f** with Bu_3SnH at 80 °C successfully afforded the corresponding β,γ-dimethyl-γ-lactams **21a** and **21f**, respectively, with trans/cis ratios 80:20 and 23:77, respectively. β-Amino radical cyclizations of **22a** and **22b** were promoted by Ph_3SnH or by Bu_3SnH at 80 °C with trans/cis ratios of 82:18 and 35:65, respectively. These trans/cis ratios were similar to those observed in the copper-catalyzed cyclization of **15b** and **15d**.

The Role of the Amine Ligand and Transition States of the Cyclization. As described in our previous papers, transition states of transition metal-catalyzed radical cyclizations are similar to those of free-radical

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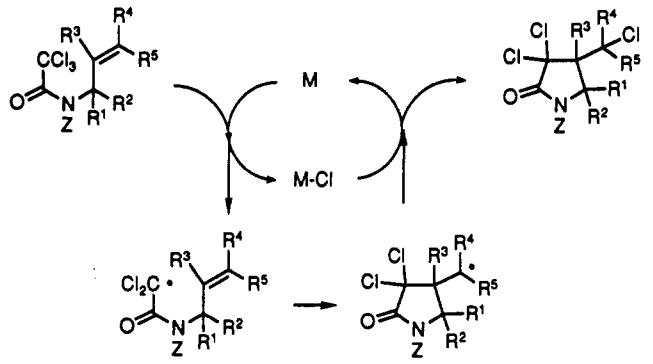
Table V. Tin-Mediated Cyclizations of 15 and 22

substrate	SnH	temp (°C)	time (h)	product	yield (%)	ratio (trans/cis)
15a	Bu_3SnH	80	17	21a	78	80:20
15f	Bu_3SnH	80	9	21f	55	23:77
22a	Ph_3SnH	80	22	23a	83	82:18
22b	Bu_3SnH	80	3	23b	95	35:65

Scheme VI



cyclizations.[2,3] The catalyst acts as a carrier of the chlorine atom by way of a redox reaction between Cu(I) and Cu(II) as shown in Scheme VI. Addition of bipyridine, TMEDA, or sparteine to CuCl produces Cu(I)–amine complexes, such as CuCl(bipyridine) or $[Cu(bipyridine)_2]^+Cl^-$. It is likely that coordination of electron-donating bidentate amine ligands to CuCl facilitates abstraction of a chlorine atom from the *N*-allyltrichloroacetamide to afford an *N*-allyldichloroacetamide radical. It is curious that the cyclization does not occur when a NH group exists either in the substrates or the ligand. In the reaction of **1a** with the CuCl/bipyridine catalyst, a green insoluble material showing a broad IR absorption around 1700 cm^{-1} was isolated. The reaction of **1b** with CuCl/ethylenediamine catalyst also produced a green insoluble material. These results indicate that the NH group in **1a** or ethylenediamine reacts with the copper catalyst to form an inactive copper–amide or copper–amine species.

The copper-catalyzed cyclizations of *N*-allyltrichloroacetamides of secondary allylic amines and the tin-mediated reductive cyclizations of analogous systems showed that either trans or cis isomers of β,γ-disubstituted γ-lactams can be prepared with good stereoselectivity by simply changing the substituents on the amide nitrogen. It is important that the cis/trans ratios of the copper- and ruthenium-catalyzed cyclizations of **15b** and **15d**, the tin-mediated reductive cyclization of **15a** and **15d**, and the tin-mediated cyclizations of **22a** and **22b** are not very different. It is likely that these three reactions proceed via similar transition states. The participation of metallic species in the carbon–carbon forming step in the metal-catalyzed cyclizations is excluded by these results. It should be possible to explain these stereochemical outcomes according to the usual transition states for free-radical cyclizations discussed by Houk[9] and Beckwith.[10] As described in the previous paper, the trans-selective cyclization of **15a** was explained by invoking envelope-shaped transition states that avoid steric repulsion between the methyl group adjacent to the amide nitrogen and the methylene moiety.[3c] Complicating the explanation of the stereochemical results described in this paper is an additional steric factor derived from the presence of the substituent on the amide nitrogen, which must be considered. Further studies are necessary to draw the probable transition states that explain why introduction of a Ts, Ms, Cbz, or Ts group on the amide nitrogen causes predominant formation of cis-γ-lactams.[11]

(9) Spellmeyer, D. C.; Houk, K. *J. Org. Chem.* **1987**, *52*, 959.
(10) Beckwith, A. L.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3295.

Experimental Section

General. All manipulations were carried out under an inert atmosphere. All solvents were distilled from drying reagents before use. NMR spectra in $CDCl_3$ are reported by δ-values (ppm) and coupling constants (J, Hz). IR spectra are reported in cm^{-1}.

General Procedure for Preparation of *N*-Alkyl-*N*-allyltrichloroacetamides. *N*-Alkyl-*N*-allyltrichloroacetamides were prepared by trichloroacetylation of the corresponding *N*-alkyl-*N*-allylamines (vide infra) in the presence of Et_3N in ether at room temperature. Spectral data for the amides are listed below. Existence of two rotational isomers around the acyl–nitrogen bond in several compounds caused line broadening of the peaks in the ^1H NMR or two separate signals in the ^{13}C NMR. The broad signals are designated as *, and the peaks derived from the other rotational isomer are reported in brackets []. NMR spectra of **1b**, **1c**, **3–7**, **15b**, and **15c** are given in the supplementary material.

1b: colorless oil; bp 79–83 °C/0.3 mmHg; ^1H NMR 3.90–4.15* [4.20–4.43*] (s, NCH_2), 5.12–5.40* [5.80–5.95*] (m, olefin); ^{13}C NMR 49.7 [51.5], 93.0, 118.1 [119.3], 131.0 [131.9], 161.0; IR (neat) 1680; HRMS calcd for $C_8H_{10}NOCl_3$ 240.9827, found 240.9787.

1c: pale yellow semisolid; mp 41–42 °C; ^1H NMR 3.95* [4.29*], 4.71* [5.00*], (s, CH_2Ph, NCH_2), 5.30*, 5.84* (m, olefin), 7.30 (Ph); ^{13}C NMR 49.5, 50.8 [52.0], 92.7, 118.0 [119.2], 127.0, 127.5, 128.3, 130.4 [131.3], 135.0, 160.2; IR (CH_2Cl_2) 1680. Anal. Calcd for $C_{12}H_{12}NOCl_3$: C, 49.26, 4.13, 5.47. Found: C, 49.27; H, 4.04; N, 4.75.

3: white semisolid; mp 38–40 °C; ^1H NMR 1.54* [1.76*] (s, Me), 3.85* [4.05*] (s, CH_2N), 4.56–4.75* [4.82–5.00*] (s, CH_2-Ph), 5.10–5.30* (s, olefin), 7.18–7.40 (Ph); ^{13}C NMR 18.0, 25.8, 45.6 [46.8], 50.0 [52.0], 93.4, 117.5, [118.7], 127.2, 127.6, 128.4, 136.0, 137.8, 160.8; IR (CH_2Cl_2) 1665. Anal. Calcd for $C_{14}H_{16}$-$NOCl_3$; C, 52.44; H, 5.03; N, 4.37. Found: C, 52.40; H, 5.03; N, 4.06.

4: white solid; mp 76–78 °C; ^1H NMR 1.96 (s, Me), 5.00–5.12 (m, CH_2Ph), 5.00, 5.07, 6.01 (olefin), 7.26–7.40 (Ph); ^{13}C NMR 25.8, 51.1, 64.2, 94.8, 111.8, 126.5, 127.1, 128.3, 138.2, 143.8, 160.4; IR (CH_2Cl_2) 1680. Anal. Calcd for $C_{14}H_{16}NOCl_3$: C, 52.44; H, 5.03; N, 4.37. Found: C, 52.39; H, 5.06; N, 4.21.

5: white solid; mp 71–72 °C; ^1H NMR 1.71–1.85, 2.25–2.53 (m, CH_2), 4.42, 4.47 (d, J = 13.5, CH_2Ph), 5.50–5.66, 5.80–5.94, 5.94–6.03 (m, olefin and NCH), 7.13–7.35 (Ph); IR (CH_2Cl_2) 1675. Anal. Calcd for $C_{14}H_{15}NOCl_3$: C, 52.77; H, 4.43; N, 4.40. Found: C, 52.89; H, 4.41; N, 4.40.

6: white solid; mp 92.5–94.0 °C; ^1H NMR 1.48–2.15 (m, CH_2), 4.35, 4.75 (d, J = 16.1, CH_2Ph), 5.25–5.40, 5.56–5.67, 5.90–6.03 (m, olefin and NCH), 7.15–7.37 (Ph); ^{13}C NMR 21.5, 24.3, 27.7, 45.3 [48.6], 57.1, 92.3 [93.5], 125.8 [126.1], 126.2 [127.1], 127.8 [128.1], 128.9, 133.0, 136.0 [137.1], 161.0 [161.9]; IR (CH_2Cl_2) 1675. Anal. Calcd for $C_{15}H_{16}NOCl_3$: C, 54.16; H, 4.85; N, 4.21. Found: C, 54.41; H, 4.93; N, 4.18.

7: white semisolid; mp 33–34 °C; ^1H NMR 1.70 (s, Me), 3.90 [4.16] (s, NCH), 4.64 [4.95] (s, CH_2Ph), 4.71, 4.89, [4.93, 5.07] (olefin); ^{13}C NMR 19.9, 50.5 (52.0), 52.2 (54.0), 92.8, 112.8, 113.5, 127.0, 127.7, 128.7, 134.5 (135.5), 138.8, 160.8; IR (CH_2Cl_2) 1680.

(11) We carried out MM2 calculations using Houk's parameters for the transition states for cyclizations of 3-aza-4-methyl-5-hexenyl radicals with a H, Me, or ^{t}Bu group as the amide substituent. The results are as follows: (1) the transition states leading to the trans isomers were more favorable than those leading to the cis isomers, and (2) the introduction of either methyl or *tert*-butyl substituents to the amide nitrogen decreased the strain energy difference between the two transition states. These results are consistent with the experimental data that introduction of methyl or benzyl substituents on the nitrogen contributes to the increase of cis-selectivity. Further MM2 studies for examining the effect of Ts, Ms, Cbz, and ^{t}Boc groups failed because of the lack of parameters.

Table VI. ^{1}H NMR Spectra (δ, J in Hz) of 2b–2e

substrate	CCl_2CH	NCH_2	$ClCH_2$	substituent on the amide
2b	3.06–3.17 (m)	3.74 (dd, J = 10.3, 11.2)	3.23 (dd, J = 8.3, 10.3)	3.97 (d, J = 4.4, allylic)
		4.00 (dd, J = 6.3, 11.2)	3.59 (dd, J = 6.8, 10.3)	5.20–5.35, 5.65–5.85 (m, olefin)
2c	3.02–3.15 (m)	3.68 (dd, J = 6.3, 11.2)	3.10 (dd, J = 8.3, 10.8)	4.45 and 4.64 (d, J = 14.7, benzyl)
		3.97 (dd, J = 3.9, 11.2)	3.47 (dd, J = 5.9, 10.8)	7.28–7.50 (m, Ph)
2d	3.30–3.14 (m)	3.93 (dd, J = 4.4, 10.3)	3.56 (dd, J = 8.8, 11.2)	2.46 (s, Me)
		4.25 (dd, J = 6.8, 10.3)	3.66 (dd, J = 8.8, 11.2)	7.38 and 7.95 (d, J = 8.3, aromatic)
2e	3.10–3.12 (m)	3.98 (dd, J = 4.4, 11.2)	3.54 (dd, J = 9.3, 11.2)	5.34 (s, benzyl)
		4.17 (dd, J = 6.8, 11.2)	3.72 (dd, J = 9.8, 11.2)	7.35–7.47 (m, Ph)

Anal. Calcd for $C_{13}H_{14}NOCl_3$: C, 50.92; H, 4.60; N, 4.57. Found: 50.99; H, 4.75; N, 4.54.

15b: colorless oil; ^{1}H NMR 1.36 (d, J = 6.8, Me), 4.26–4.35*, 4.68–4.80* (d, J = 16.1, CH_2Ph), 5.21–5.45*, 5.90–6.10* (m, olefin and NCH); IR (CH_2Cl_2) 1675. Anal. Calcd for $C_{13}H_{14}NOCl_3$: C, 50.92; H, 4.60; N, 4.57. Found: C, 50.94; H, 4.64; N, 4.18.

15c: colorless oil; ^{1}H NMR 1.20–1.40* (m, NCH*Me*), 2.78* [3.11*] (s, NMe), 5.07–5.29*, 5.70–5.90* (m, olefin and NCH); IR (CH_2Cl_2) 1680. Anal. Calcd for $C_7H_{10}NOCl_3$: C, 36.47; H, 4.37; N, 6.08. Found: C, 36.49; H, 4.46; N, 5.89.

Preparation of *N*-Allyltrichloroacetamide with Tosyl, Mesyl, Cbz, and t-Boc Substituents on the Amide. Introductions of tosyl, mesyl, Cbz, and t-Boc groups onto *N*-allylamines were carried out by standard methods for the protection of amine functions.[12] Trichloroacetylations of these amides or urethanes were carried out by acetylation the corresponding lithium amide with CCl_3COCl. Because of the instability of the amides obtained to both acid and base, careful workup was required to avoid decomposition. In a typical example, a hexane solution of n-BuLi (1.67 N, 1.7 mmol, 2.8 mL) was added to a solution of *N*-allyltosylamide (0.6 g, 2.8 mmol) in THF (14 mL) at −78 °C, and the solution was stirred at this temperature for 0.5 h. Trichloroacetyl chloride (0.3 mL, 546 mg, 3 mmol) was added, and the mixture was stirred for 2 h. Excess base was quenched with saturated NH_4Cl, and the mixture was quickly extracted with ether. The extracts were washed with 1 N NaOH and brine, dried over $MgSO_4$, and concentrated. Chromatographic purification (silica gel, hexane/ether) of the residue at −78 °C gave **1d** (1.0 g, 99%).

1d: white solid; mp 74–76 °C; ^{1}H NMR 2.45 (s, Me of tosyl group), 4.92 (d, J = 5.4, NCH), 5.38, 5.46, 5.95 (olefin), 7.34 and 7.93 (aromatic); IR (CH_2Cl_2) 1705. Anal. Calcd for $C_{12}H_{12}NOSCl_3$: C, 40.41; H, 3.39; N, 3.93. Found: C, 40.58; H, 3.46; N, 3.84.

1e: slightly yellow oil; ^{1}H NMR 4.35 (d, J = 5.9, NCH_2), 5.26 (s, CH_2Ph), 5.21, 5.25, 5.86 (olefin), 7.38 (Ph); IR (CH_2Cl_2) 1760, 1710. Anal. Calcd for $C_{13}H_{12}NOCl_3$: C, 46.39; H, 3.60; N, 4.16. Found: C, 46.51; H, 3.73; N, 4.07.

15d: white solid; mp 96.5–98 °C; ^{1}H NMR 1.89 (d, J = 6.3 Me), 2.45 (Me of tosyl group), 5.40–5.50 (m, NCH), 5.38, 5.41, 6.38 (olefin), 7.33, 7.92 (aromatic); ^{13}C NMR 19.0, 21.4, 59.1, 92.3, 117.2, 128.9, 129.0, 135.3, 136.4, 144.8, 158.5; IR (CH_2Cl_2) 1700. Anal. Calcd for $C_{13}H_{14}NSO_3Cl_3$: C, 42.12; H, 3.81; N, 3.78. Found: C, 42.16; H, 3.79; N, 3.63.

15e: white solid; mp 96–97 °C; ^{1}H NMR 1.77 (d, J = 6.8, Me), 3.40 (mesyl), 5.37–5.42 (m, NCH), 5.30, 5.36, 6.24 (olefin); ^{13}C NMR 18.9, 43.9, 59.4, 92.1, 117.5, 136.0, 160.7; IR (CH_2Cl_2) 1700. Anal. Calcd for $C_7H_{10}NO_3Cl_3$: C, 28.54; H, 3.42; N, 4.75. Found: C, 28.63; H, 3.41; N, 4.64.

15f: colorless oil; ^{1}H NMR 1.45 (d, J = 6.8, Me), 4.90 (m, NCH), 5.23 (s, CH_2Ph), 5.19, 5.25, 5.99 (olefin), 7.35 (Ph); IR (CH_2Cl_2) 1760, 1710. Anal. Calcd for $C_{14}H_{14}NOCl_3$: 47.96; H, 4.02; N, 3.99. Found: C, 47.86; H, 4.12; N, 3.48.

15g: colorless oil; ^{1}H NMR 1.45 (d, J = 6.8 Me), 1.53 (s, t-Bu), 4.87 (m, NCH), 5.20, 5.25, 6.00 (olefin); IR (CH_2Cl_2) 1760, 1715. Anal. Calcd for $C_{11}H_{16}NOCl_3$: C, 41.73; H, 5.03; N, 4.42. Found: 42.03; H, 5.31; N, 3.86.

17b: colorless oil; ^{1}H NMR 0.91 (t, J = 6.8 Me), 1.28–1.52, 1.65–1.95 (m, CH_2), 4.71 (m, NC*H*), 5.23 (s, CH_2Ph), 5.18, 5.24, 5.98 (olefin), 7.36 (Ph); IR (CH_2Cl_2) 1765, 1715. Anal. Calcd for $C_{16}H_{18}NOCl_3$: C, 50.75; H, 4.79; N, 3.70. Found: C, 50.90; H, 4.87; N, 3.56.

(12) Greene, T. W.; Wuts, P. G. *Protective Groups in Organic Synthesis*; John Willey and Sons: New York, 1991.

19b: colorless oil; ^{1}H NMR 0.86 (t, J = 7.3, CH_2*Me*), 1.30–1.45 (m, CH_2Me), 1.42 (d, J = 6.8, NCH*Me*), 1.97 (q, J = 7.3, CH_2Et), 4.87 (quint, J = 6.8, NCH), 5.22 (s, OCH_2Ph), 5.55–5.72 (olefin), 7.36 (Ph); IR (CH_2Cl_2) 1760, 1710. Anal. Calcd for $C_{17}H_{20}NO_3Cl_3$: C, 51.99; H, 5.13; N, 3.57. Found: C, 51.67; H, 5.39; N, 3.38.

Preparation of Allylamines. Three reactions were used for the preparation of allylamine precursors. (1) *N-Alkylation of amines by organic halides*: *N*-Allylbenzylamine was prepared by the reaction of allylamine with benzyl chloride according the procedure used to synthesize *N*-benzylaniline.[13] *N*-Benzylprenylamine and *N*-benzylmethallylamine were prepared from benzylamine and prenyl bromide or methallyl chloride. In a typical example, a mixture of allylamine (25 g, 0.44 mol), $NaHCO_3$ (11.5 g, 0.14 mol), water (44 mL), and benzyl chloride (13.9 g, 0.11 mol) was heated at 90–95 °C for 4 h. Workup similar to that used for the preparation of *N*-benzylaniline,[13] followed by distillation (45 °C/1 mmHg), gave *N*-allylbenzylamine in 54% yield. (2) *Palladium-catalyzed allylic amination*:[14] Precursors of **4–6** were prepared by palladium-catalyzed substitution reaction of methyl prenyl carbonate, methyl 2-cyclopentyl carbonate, or methyl 2-cyclohexyl carbonate with benzylamine. In a typical example, a mixture of methyl prenyl carbonate (2 g, 13.9 mmol), $(DBA)_3Pd_2{\cdot}CHCl_3$ (354 mg, 0.23 mmol), PPh_3 (364 mg), and benzylamine (1.44 g, 13.9 mmol) in acetonitrile (65 mL) was heated under reflux for 2 h. After removal of insoluble materials by filtration, the solution was concentrated. The crude amine was subjected to trichloroacetylation to afford **4** in 41% yield. Compound **4** was contaminated by a small amount of regioisomer **3**, but **3** could be removed by a silica gel column. (3) *Hydrolysis of N-allyltrichloroacetamides*: 3-Amino-1-butene, 3-amino-1-heptene, and 2-amino-4-heptene were prepared by hydrolysis of the corresponding trichloroacetamides, which were synthesized by the Overman rearrangement.[15] *N*-Benzyl-3-amino-1-butene and *N*-methyl-3-amino-1-butene were prepared by $LiAlH_4$ reduction of benzamide and the formamide of 3-amino-1-butene, respectively.

Detailed procedures are described in the supplementary material.

General Procedures for the Cyclization of *N*-Allyltrichloroacetamides. Procedures using $RuCl_2(PPh_3)_3$ or CuCl as the catalyst have been reported elsewhere.[3a,3c] For the cyclizations with CuCl/bipyridine catalyst, the experiments must be carried out carefully to avoid contact with air to obtain the lactams in high yields. Typically, **1b** (50 mg, 0.206 mmol) and CuCl (6.1 mg, 0.062 mmol, 30 mol %) were measured into a 10-mL flask, and the atmosphere was replaced by argon. Then, carefully degassed dichloromethane (1.2 mL) was added. To this suspension was added 2,2′-bipyridine (9.7 mg, 0.206 mmol) dissolved in 0.5 mL of degassed dichloromethane, and the mixture was stirred for 2 h at room temperature. The white copper salts instantly dissolved, and a brown homogeneous solution formed. The brown solution gradually turned to a green, turbid solution. The resulting mixture was transferred to the head of a short silica gel column eluted with dichloromethane. Compound **2b** was obtained in 98% yield (49 mg). ^{1}H NMR spectra of **2b–2e** are shown in Table VI. Other data are given below.

(13) Wilson, F. G.; Wheeler, T. S. *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. 1, p 102.

(14) Trost, B. M.; Keinan, E. *J. Org. Chem.* **1979**, *44*, 3451. Hayashi, T.; Kanehira, K.; Hagihara, T.; Kumada, M. *Ibid.* **1988**, *53*, 113. For a extensive review; Tsuji, J. *Tetrahedron* **1986**, *42*, 4361.

(15) Overman, L. E. *J. Am. Chem. Soc.* **1976**, *98*, 2901.

Table VII. ^{1}H NMR Spectra (δ, J in Hz) of 16b–16g

substrate	CCl_2CH	NH H2	CH_2Cl	Me and N-substituent
16b (cis)	3.12 (ddd, J = 3.9, 6.4, 10.8)	3.67 (qu, J = 6.4)	3.80 (dd, J = 10.8, 11.8), 4.00–4.15 (m)	1.38 (d, J = 6.8, Me), 4.09 and 5.03 (d, J = 15.1, benzyl), 7.20–7.44 (m, Ph)
16b (trans)	2.73 (ddd, J = 5.4, 6.8, 7.8)	3.31 (qu, J = 6.8)	3.66 (dd, J = 7.8, 12.2), 4.00 (dd, J = 5.4, 12.2)	1.40 (d, J = 6.8, Me), 4.03 and 5.12 (d, J = 15.1, benzyl), 7.20–7.44 (m, Ph)
16c (cis)	3.16–3.24 (m)	3.16–3.24 (m)	3.66–3.88 (m, 2 H)	1.37 (d, J = 6.8, Me), 2.99 (s, NMe)
16c (trans)	2.72 (ddd, J = 5.4, 6.8, 7.8)	3.47 (qu, J = 6.8)	3.75 (dd, J = 7.8, 12.2), 4.04 (dd, J = 5.4, 12.2)	1.48 (d, J = 6.8, Me), 2.92 (s, NMe)
16d (cis)	3.21 (ddd, J = 3.9, 6.8, 10.8)	4.69 (qu, J = 6.8)	3.78 (dd, J = 10.7, 11.7), 3.94 (dd, J = 5.4, 11.7)	1.60 (d, J = 6.8, Me), 2.46 (s, Me of tosyl), 7.38 and 7.98 (d, J = 8.3, aromatic)
16d (trans)	2.81 (ddd, J = 5.4, 6.8, 7.8)	4.25 (qu, J = 6.8)	3.63 (dd, J = 7.8, 11.7), 3.94 (dd, J = 5.4, 11.7)	1.78 (d, J = 6.8, Me), 2.46 (s, Me of tosyl), 7.38 and 7.98 (d, J = 8.3, aromatic)
16e (cis)	3.33 (ddd, J = 4.4, 6.8, 10.7)	4.62 (qu, J = 6.8)	3.82 (dd, J = 10.7, 11.7), 4.04 (dd, J = 4.4, 11.7)	1.60 (d, J = 6.8, Me), 3.39 (s, Ms)
16e (trans)	2.95 (ddd, J = 4.4, 6.8, 7.8)	4.26 (qu, J = 6.8)	3.80 (dd, J = 7.8, 11.7), 3.98 (dd, J = 4.4, 11.7)	1.76 (d, J = 6.8, Me), 3.35 (s, Ms)
16f (cis)	3.20 (ddd, J = 3.9, 6.8, 10.8)	4.53 (qu, J = 6.8)	3.82 (dd, J = 10.8, 11.8), 4.03 (dd, J = 3.9, 11.8)	1.49 (d, J = 6.8, Me), 5.33 and 5.40 (d, J = 12.7, benzyl), 7.35–7.48 (m, Ph)
16f (trans)	2.82 (dt, J = 5.4, 6.4)	4.12 (qu, J = 6.8)	3.69 (dd, J = 6.4, 11.7), 3.99 (dd, J = 7.3, 11.7)	1.61 (d, J = 6.4, Me), 5.34 and 5.41 (d, J = 12.7, benzyl), 7.35–7.48 (m, Ph)
16g (cis)	3.19 (ddd, J = 4.0, 6.8, 10.8)	4.46 (qu, J = 6.8)	3.83 (dd, J = 10.8, 11.8), 4.04 (dd, J = 4.0, 11.8)	1.48 (d, J = 6.8, Me), 1.57 (s, t-Bu)
16g (trans)	2.79 (ddd, J = 5.4, 6.4, 7.3)	4.95–5.05 (m)	3.69 (dd, J = 7.3, 11.7), 4.00 (dd, J = 5.4, 11.7)	1.61 (d, J = 6.4, Me), 1.57 (s, t-Bu)

2b: colorless oil; ^{13}C NMR 40.6, 45.9, 46.9, 51.1, 83.3, 119.2, 130.0, 165.2; IR (CH_2Cl_2) 1720. Anal. Calcd for $C_8H_{10}NOCl_3$: C, 39.62; H, 4.16; N, 5.78. Found: C, 39.71; H, 4.15; N, 5.69.

2c: white solid; mp 88.5–89.5 °C; ^{13}C NMR 40.7, 46.9, 47.5, 51.2, 83.3, 127.8, 128.0, 128.7, 134.1, 165.6; IR (CH_2Cl_2) 1725. Anal. Calcd for $C_{12}H_{12}NOCl_3$: C, 49.26; H, 4.13; N, 4.79. Found: C, 49.31; H, 4.13; N, 4.80.

2d: white solid; mp 160 °C; ^{13}C NMR 21.5, 39.8, 47.1, 50.3, 82.3, 127.9, 130.0, 132.9, 146.0, 162.6; IR (CH_2Cl_2) 1765. Anal. Calcd for $C_{12}H_{12}NOSCl_3$: C, 40.41; H, 3.39; N, 3.93. Found: C, 40.42; H, 3.45; N, 3.33.

2e: white solid; mp 80–81 °C; ^{13}C NMR 39.9, 46.2, 49.7, 68.9, 82.5, 127.8, 127.9, 128.0, 128.3, 133.9, 150.1, 162.9; IR (CH_2Cl_2) 1800, 1770, 1730; HRMS calcd for $C_{13}H_{12}NO_3Cl_3$ 338.9825, found 338.9827.

9: white solid; mp 73–75 °C; ^{1}H NMR 1.87, 1.88 (s, Me), 3.17 (dd, J = 7.1, 9.4, CCl_2CH), 3.45 (dd, J = 7, 10, NCH), 3.49 (t, J = 10, NCH), 4.49, 4.63 (d, J = 14.7, CH_2Ph), 7.24–7.37 (Ph); ^{13}C NMR 29.7, 33.3, 45.4, 47.7, 59.1, 68.6, 82.7, 128.0, 128.1, 128.9, 134.5, 165.9; IR (CH_2Cl_2) 1730. Anal. Calcd for $C_{14}H_{16}NOCl_3$: C, 52.44; H, 5.03; N, 4.37. Found: C, 51.97; H, 5.06; N, 4.24.

10: white solid; mp 104.5–105.5 °C; ^{1}H NMR 1.19 and 1.41 (s, Me), 2.96 (dd, J = 5.4, 8.8, CCl_2CH), 3.83 (dd, J = 8.8, 11.7, ClCH), 4.07 (dd, J = 5.4, 11.7, ClCH), 4.52, 4.60 (d, J = 13.5, CH_2Ph), 7.27–7.35 (Ph); ^{13}C NMR 20.0, 28.5, 38.7, 43.5, 60.0, 61.8, 82.8, 127.3, 127.4, 128.5, 136.9, 165.4; IR (CH_2Cl_2) 1720. Anal. Calcd for $C_{14}H_{16}NOCl_3$: C, 52.44; H, 5.03; N, 4.37. Found: C, 52.36; H, 5.04; N, 4.25.

11: colorless oil; ^{1}H NMR 1.77–2.08 (m, 4 H, CH_2), 3.41 (dd, J = 3.9, 6.8, Cl_2CCH), 3.92, 4.93 (d, J = 14.7, CH_2Ph), 3.99 (t, J = 6.8, NCH), 4.45 (dd, J = 3.9, 6.8, ClCH), 7.10–7.30 (Ph); IR (CH_2Cl_2) 1725. Anal. Calcd for $C_{14}H_{14}NOCl_3$: C, 52.77; H, 4.43; N, 4.40. Found: C, 52.78; H, 4.47; N, 3.93.

12: white solid; mp 83–84 °C; ^{1}H NMR 1.50–1.80, 1.90–2.10, 2.30–2.43 (m, CH_2), 3.20 (dd, J = 3.9, 8.6, Cl_2CCH), 3.75–3.85 (m, ClCH), 4.17, 4.94 (d, J = 14.7, CH_2Ph), 4.72 (dd, m, NCH), 7.22–7.40 (Ph); ^{13}C NMR 16.6, 25.5, 31.3, 45.2, 52.0, 54.6, 55.0, 82.2, 127.6, 127.8, 128.5, 134.4, 165.3; IR (CH_2Cl_2) 1720. Anal. Calcd for $C_{15}H_{16}NOCl_3$: C, 54.16; H, 4.85; N, 4.21. Found: C, 54.17; H, 4.87; N, 4.24.

13: colorless oil; ^{1}H NMR 1.36 (s, Me), 3.02, 3.35 (d, J = 10.2, $ClCH_2$), 3.64, 3.71 (d, J = 11.4, NCH_2), 4.48, 4.56 (d, J = 14.4, CH_2Ph), 7.20–7.38 (Ph); ^{13}C NMR 19.0, 47.6, 47.8, 49.4, 52.2, 89.2 128.0, 128.1, 128.7, 134.2, 165.5; IR (CH_2Cl_2) 1725. Anal. Calcd for $C_{13}H_{14}NOCl_3$: C, 50.92; H, 4.60; N, 4.57. Found: C, 51.01; H, 4.63; N, 4.53.

Preparation of *N*-Allyl-*N*-benzyldichloroacetamide (8). Amide 8 was prepared by dichloroacetylation of N-allylbenzylamine with CCl_2HCOCl and Et_3N in ether: pale yellow oil; ^{1}H NMR (1:2 mixture of rotational isomers) 4.00 (d, NCH_2), 4.63 [4.71] (s, CH_2Ph), 5.10–5.32, 5.68–5.86 (olefin), 6.20 [6.25] (s, Cl_2CH), 7.17–7.42 (Ph). IR (CH_2Cl_2) 1680. Anal. Calcd for $C_{12}H_{13}NOCl_2$: C, 55.83; H, 5.08; N, 5.43. Found: C, 55.79; H, 5.05; N, 5.17.

Cyclization of 8. A mixture of 8 (50 mg, 0.19 mmol) and CuCl (5.8 mg, 0.06 mmol) was suspended in degassed dichloroethane (1.1 mL). To this suspension was added 2,2′-bipyridine (9.1 mg, 0.06 mmol) dissolved in degassed dichloroethane (0.5 mL). The mixture was heated at 80 °C for 4 h. Purification of the reaction mixture on a silica gel column with CH_2Cl_2 afforded the desired lactam 14 (colorless oil; 49.5 g, 99%) as a diastereomeric mixture: ^{1}H NMR 2.77–2.96 (m, ClHCC*H*), 3.13–3.21, 3.33–3.47 (m, $ClCH_2$), 3.54–3.81 (m, NCH_2), 4.38–4.62 (m, COClCH and CH_2Ph), 7.21–7.40 (Ph); IR (CH_2Cl_2) 1705. Anal. Calcd for $C_{12}H_{13}NOCl_3$: C, 55.83; H, 5.08; N, 5.43. Found: C, 56.06; H, 5.31; N, 5.34.

Stereoselective Cyclization of *N*-(1-Buten-3-yl)trichloroacetamide Derivatives: The cyclization of **15a–15g** were carried out according to the general procedure described above. The physical and spectral data reported are those of a mixture of cis and trans isomers unless otherwise noted. ^{1}H NMR spectra are summarized in Table VII.

16b: colorless oil; ^{13}C NMR trans isomer 17.1, 40.1, 44.1, 53.9, 57.8, 83.4, 127.5, 127.7, 128.6, 134.2, 165.1; cis isomer 15.5, 38.7, 45.5, 48.8, 52.3, 82.6, 127.5, 127.7, 128.6, 134.2, 161.8; IR (CH_2Cl_2) 1725. Anal. Calcd for $C_{13}H_{14}NOCl_3$: C, 50.92; H, 4.60; N, 4.57. Found: C, 50.93; H, 4.76; N, 4.38.

16c: white solid; mp 65–66 °C; IR (CH_2Cl_2) 1720. Anal. Calcd for $C_7H_{10}NOCl_3$: C, 36.47; H, 4.37; N, 6.08. Found: C, 36.43; H, 4.43; N, 5.31.

16d: white solid; mp 165–167 °C; ^{13}C NMR cis isomer 13.7, 21.4, 37.8, 53.5, 55.0, 81.1, 128.3, 129.5, 134.0, 145.8, 162.8; IR (CH_2Cl_2) 1760. Anal. Calcd for $C_{13}H_{14}NSO_3Cl_3$: C, 42.12; H, 3.81; N, 3.78. Found: C, 41.97; H, 3.61; N, 3.81.

16d: white solid; mp 165–167 °C; ^{13}C NMR cis isomer 13.7, 21.4, 37.8, 53.5, 55.0, 81.1, 128.3, 129.5, 134.0, 145.8, 162.8; IR (CH_2Cl_2) 1760. Anal. Calcd for $C_{13}H_{14}NSO_3Cl_3$: C, 42.12; H, 3.81; N, 3.78. Found: C, 41.97; H, 3.61; N, 3.81.

16e: white solid; mp 85–87 °C; ^{13}C NMR trans isomer 20.6, 37.8, 41.8, 56.0, 57.0, 81.6, 164.4; cis isomer 13.6, 37.7, 41.6, 53.5, 54.7, 80.9, 164.1; IR (CH_2Cl_2) 1755. Anal. Calcd for $C_7H_{10}NO_3Cl_3$: C, 28.54; H, 3.42; N, 4.75. Found: C, 28.76; H, 3.51; N, 4.86.

16f: white solid; mp 93 °C; IR (CH_2Cl_2) 1800, 1770, 1735. Anal. Calcd for $C_{14}H_{14}NOCl_3$: C, 47.96; H, 4.02; N, 3.99. Found: C, 48.13; H, 4.02; N, 3.89.

16g: colorless oil; IR (CH_2Cl_2) 1800, 1770, 1735. Anal. Calcd for $C_{11}H_{16}NOCl_3$: C, 41.73; H, 5.03; N, 4.42. Found: C, 41.70; H, 5.15; N, 4.37.

18b (cis:trans = 37:63): colorless oil; ^{1}H NMR trans isomer 0.93 (t, J = 7.3, Me), 1.20–1.50, 1.65–2.10 (m, CH_2), 3.03 (ddd, J = 3.9, 4.9, 7.8, Cl_2CCH), 3.60 (dd, J = 7.8, 11.7, ClCH), 3.94 (dd, J = 4.9, 11.7, ClCH), 4.16 (dt, J = 3.9, 7.3, NCH), 5.27, 5.38 (d, J = 13.5, CH_2Ph), 7.28–7.46 (Ph); cis isomer 3.32 (ddd, J = 3.9, 7.3, 10.8, Cl_2CCH), 3.82 (dd, J = 10.8, 11.7, ClCH), 4.03 (dd, J

= 3.9, 11.7, ClCH), 4.50 (dt, J = 5.4, 7.3; NCH), 7.26–7.46 (Ph); IR (CH_2Cl_2) 1800, 1775, 1735. Anal. Calcd for $C_{16}H_{18}NO_3Cl_3$: C, 50.75; H, 4.79; N, 3.70. Found: C, 50.35; H, 4.70; N, 3.73.

20b (a mixture of diastereomers): colorless oil; ^{1}H NMR (major isomer) 1.01 (t, J = 7.3, CH_2Me), 1.48–1.97, 2.27–2.40 (m, CH_2), 3.10 (dd, J = 7.3, 10.0, Cl_2CCH), 4.23 (dt, J = 2.7, 10.0, ClCH), 4.30–4.50 (m, NCH), 5.31 and 5.38 (d, J = 13.5, CH_2Ph), 7.30–7.50 (Ph); ^{13}C NMR (major isomer) 13.1, 13.4, 19.1, 37.0, 54.5, 56.0, 59.2, 69.1, 81.7, 128.1, 128.4, 128.6, 134.4, 150.0, 163.9; IR (CH_2Cl_2) 1810, 1780, 1740. Anal. Calcd for $C_{17}H_{20}NO_3Cl_3$: C, 51.99; H, 5.13; N, 3.57. Found: C, 50.62; H, 5.18; N, 3.69.

Tin-Mediated Cyclization of 15a and 15f. A mixture of **15a** (50 mg, 0.16 mmol), Bu_3SnH (0.17 mL, 0.19 g, 0.65 mmol), and AIBN (14 mg, 0.08 mmol) was heated in benzene under reflux for 9 h. KF (110 mg, 1.9 mmol) was added to the cooled solution, and the mixture was stirred overnight at room temperature. After filtration, the filtrate was concentrated, and the residue was purified on a silica gel column (elution; hexane/ether) to afford **21a** as colorless oil (26 mg, 79%). The spectra data of **21a** have been reported previously.[3c] By a similar procedure, **21f** was obtained from **15f**.

21f: white solid; ^{1}H NMR trans isomer 1.03 (d, J = 6.8, β-Me), 1.15 (d, J = 6.8, γ-Me), 1.92 (m, $COCH_2CH$), 2.09 (dd, J = 7.8, 16.6, COCH), 2.64 (dd, J = 8.3, 16.6, COCH), 3.03 (quint, J = 6.8, NCH), 3.97, 4.96 (d, J = 15.1, CH_2Ph), 7.20–7.36 (m, 5 H, Ph); cis isomer 0.99 (d, J = 6.8, β-Me), 1.15 (d, J = 6.8, γ-Me), 2.16 (dd, J = 8.3, 15.1, COCH), 2.35–2.58 (m, $COCH_2CH$), 2.53 (dd, J = 7.8, 15.1, COCH), 3.49 (quint, J = 6.8, NCH), 3.93 and 4.99 (d, J = 15.1, CH_2Ph), 7.20–7.36 (Ph); IR (CH_2Cl_2) 1680. Because of contamination by tin products, an analytically pure sample was not obtained.

Preparation of *N*-(2-Chloroethyl)-*N*-(1-buten-3-yl)benzylamine (22a). Compound **22a** was prepared by hydroxyethylation[15] of *N*-(1-buten-3-yl)benzylamine with ethylene oxide, prepared in situ from 2-bromoethanol and NaOMe in methanol, followed by displacement of the hydroxy group by a chlorine atom with MsCl[16] (57% from *N*-(1-buten-3-yl)benzylamine): colorless oil; ^{1}H NMR 1.15 (d, J = 6.8, Me), 2.75 and 2.85 (dt, J = 6.8, 10.8, NCH_2CH_2Cl), 3.25–3.42 (m, CH_2Cl and CHN), 3.62, 3.68 (d, J = 14.2; CH_2Ph), 5.09, 5.15, 5.88 (olefin), 7.20–7.40 (Ph); IR (neat) 680, 720; HRMS calcd for $C_{13}H_{18}NCl$ 223.1129, found 223.1127.

Preparation of *N*-(2-Bromoethyl)-*N*-(1-buten-3-yl)-*p*-toluenesulfonamide (22b). Bromoethylation of *N*-(1-buten-3-yl)-tosylamide was carried out according the process reported by Padwa:[8a] white solid; mp 38–40 °C; ^{1}H NMR 1.16 (d, J = 6.8, 3 H, Me), 2.43 (Me of tosyl group), 3.24–3.61 (m, $BrCH_2CH_2N$), 4.51 (dq, J = 2.6, 6.8, NCH), 5.08, 5.14, 5.58 (olefin), 7.32, 7.73 (aromatic); IR (CH_2Cl_2) 1355, 1155. Anal. Calcd for $C_{13}H_{18}NO_2SBr$: C, 46.99; H, 5.46; N, 4.22. Found: C, 47.01; H, 5.52; N, 4.08.

Cyclization of 22a and 22b. A mixture of **22a** (25 mg, 0.10 mmol), Ph_3SnH (40 mg, 0.11 mmol), and AIBN (9 mg, 0.05 mmol) was heated in toluene (5 mL) at 80 °C for 22 h. A workup similar to that used in the tin-mediated cyclization of **15b** afforded **23a** as colorless oil (18 mg, 72%). Because of the difficulty in removing a small amount of tin reside from **23a**, an analytically pure sample was not obtained. The cyclization of **22b** was done with Bu_3SnH instead of Ph_3SnH to give **23b** in 89% yield.

23a: colorless oil; ^{1}H NMR trans isomer; 0.96 (d, J = 6.8, Me), 1.04 (d, J = 6.8, NCH*Me*), 1.78–2.02, 2.25–2.20, 2.85–2.95 (m, CH_2 and CH), 3.21, 4.05 (d, J = 12.9, CH_2Ph), 7.30–7.75 (Ph); cis isomer 0.99 (d, J = 6.8, Me), 1.20 (d, J = 6.8, Me), 1.78–2.02, 2.15–2.20, 3.66–3.75 (m, CH_2 and CH), 3.41, 3.96 (d, J = 12.9, CH_2Ph), 7.30–7.75 (Ph); IR (neat) 1430, 730, 695.

23b: white solid; mp 49–51 °C; ^{1}H NMR trans isomer 0.68 (d, J = 6.8, Me), 1.06–1.16 (m, NCHC*H*Me), 1.35 (d, J = 6.8, NCH*Me*), 1.76–1.94 (m, NCH_2CH_2), 2.43 (Me of tosyl group), 3.12 (quint, J = 6.8, NC*H*Me), 3.26–3.43 (m, NCH_2), 7.30, 7.72 (aromatic); cis isomer 0.89 (d, J = 6.8, Me), 1.15 (d, J = 6.8, NCH*Me*), 1.03–1.30 (m, NCH), 1.70–1.94 (m, NCH_2), 2.43 (Me of tosyl group), 3.03 (dt, J = 6.8, 9.8, NCH_2), 3.70 (quint, J = 6.8, NC*H*Me), 7.30, 7.72 (aromatic); IR (CH_2Cl_2) 1330, 1160. Anal. Calcd for $C_{13}H_{19}NO_2S$: C, 61.63; H, 7.56; N, 5.53. Found: C, 61.83; H, 7.15; N, 5.34.

Determination of the Stereochemistry of the β,γ-Disubstituted γ-Lactams or 4,5-Disubstituted Pyrrolidines. Assignments of cis and trans isomers of **16a**, **18a**, **20a**, **21a**, and their derivatives have been reported in our previous paper.[3c] Stereochemically equivocal compounds in this paper were subjected to chemical transformation to authentic samples, which were prepared from **16a**, **18a**, **20a**, and **21a**.

Preparation of *cis*-16a from 16g. Deprotection of **16g** was carried out with 1 N HCl at room temperature for 2 days (48%).

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Supplementary Material Available: Detailed data for the cyclization of **1a–1e** and **15a–15g**, detailed experimental procedures including spectral data for synthetic intermediates, ^{1}H and ^{13}C NMR spectra of **1b**, **1c**, **3–5**, and **2e**, and ^{1}H NMR spectra of **6**, **15b**, **15c**, and **22a** (22 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfiche version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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