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Palladium-Catalyzed Ring-Opening Reactions of 1-Acetyl-4-vinyl-2-azetidinones and 1-Sulfonyl-2-vinylazetidines. Role of Intramolecular Participation of Amide Anion

Akiharu Satake, Hideo Ishii, Isao Shimizu*, Yoichi Inoue, Hajime Hasegawa, and Akio Yamamoto

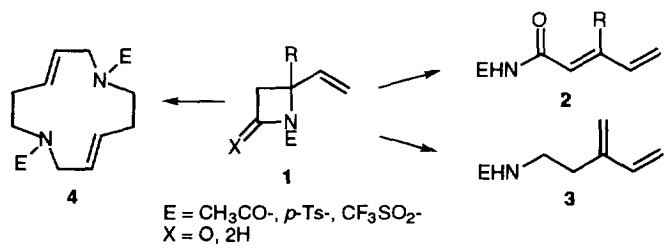
Department of Applied Chemistry, School of Science and Engineering, Waseda University, 3-4-1 Okubo, Shinjuku-ku, Tokyo 169

Abstract: Ring opening reactions of 1-acetyl-4-vinyl-2-azetidinones in the presence of palladium(0)-*n*-Bu_3P catalyst gave 2,4-pentadienamides in good yields, whereas 2-substituted-1,3-dienes were produced by the reaction of 1-sulfonyl-2-vinyl-2-methylazetidines. Ring opening dimerization took place to give 1,7-ditrifluoromethanesulfonyl-1,7-diazacyclododecane in the reaction of 1-trifluoromethanesulfonyl-2-vinylazetidine.

Introduction

Efficient synthesis of nitrogen containing organic molecules is of considerable interest in organic synthesis. 4-Vinyl-2-azetidinone and 2-vinylazetidines are considered to be useful starting materials for nitrogen containing organic molecules in view of their ready accessibility by [2+2] cycloaddition of chlorosulfonyl isocyanate (CSI) and butadiene or isoprene[1]. However, selective ring opening reaction of azetidines has been scarcely reported[2]. Oshima reported that the ring opening reaction of 2-(1,3-butadienyl)-azetidines can be carried out with palladium catalysts to give vinylpiperidine derivatives. In the course of our synthetic studies to utilize 2-vinylazetidines and their derivatives with palladium catalysts, we have found that the selectivity of the ring opening reaction depends on the structure of the substrate. In this paper we describe the selective ring opening reaction of 1-substituted 4-vinyl-2-azetidinones and 2-vinylazetidines **1** to give a variety of products, **2**, **3**, or **4** depending on the nature of the substrate and reaction conditions (Scheme 1).

Scheme 1

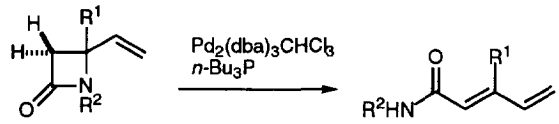


Results

Reaction of 4-vinyl-2-azetidinones

Reaction of 1-acetyl-4-vinyl-2-azetidinones (**5**, **6**) with $Pd_2(dba)_3CHCl_3$ (2.5 mol%) and *n*-Bu_3P (10 mol%) in DMSO at 120 °C gave *N*-acetyl-3-methyl-2,4-pentadienamide (**9**) and *N*-acetyl-2,4-pentadienamide (**10**). No cyclization reaction to give piperidine derivatives was observed. The results are summarized in Table 1. The reaction of **5** proceeded smoothly in DMSO and DMF to give **9** in 88% and 86% yield, respectively, as a 1:1 mixture of *E* and *Z* isomers (Runs 1 and 2), whereas no reaction took place in dioxane or toluene. Only *E* isomer was obtained in the reaction of **6** in 74% yield (Run 5). The attachment of the acetyl group on the

nitrogen atom is important for the reaction. No reaction proceeded with **7**[1] having no substituent or with **8** having the benzyl group on the nitrogen atom.



5 R^1 = Me, R^2 = Ac
6 R^1 = H, R^2 = Ac
7 R^1 = Me, R^2 = H
8 R^1 = Me, R^2 = Bn

9 R^1 = Me, R^2 = Ac
10 R^1 = H, R^2 = Ac

Table 1

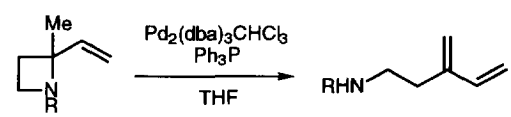
Run	R^1	R^2	Solvent	Temp. (°C)	Product	Yield (%)[a]
1	Me	Ac	DMSO	120	**9**	88[b]
2			DMF	110	**9**	86[b]
3			dioxane	reflux	-	0
4			toluene	reflux	-	0
5	H	Ac	DMSO	120	**10**	74
6			DMF	110	**10**	42
7	Me	H	DMSO	120	-	0
8	Me	Bn	DMSO	120	-	0

a) isolated yield. b) *E* / *Z* = 1 / 1

Reaction of N-sulfonyl-4-vinyl-2-azetidines

In contrast to the above results, introduction of the sulfonyl groups on the azetidine nitrogen atom and removal of the carbonyl group caused the change in the reaction course as shown in Scheme 2, where the hydrogen was abstracted from the methyl substituent, not from the methylene group. Reaction of **11** and **12** in the presence of $Pd_2(dba)_3CHCl_3$ and PPh_3 at room temperature gave **13** and **14** in 77% yields, respectively.

Scheme 2

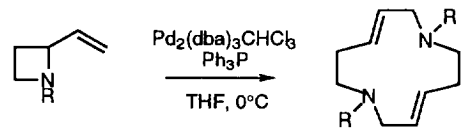


11 R = Ts
12 R = Tf

13 R = Ts 77 %
14 R = Tf 77 %

Interestingly, for the *N*-sulfonyl-vinylazetidines without the methyl substituent (**15** in Scheme 3) the palladium-catalyzed reaction gave an entirely different product **17**, a cyclic dimer of **15**, in 95 % yield. Trifluoromethanesulfonyl group was essential for the dimerization reaction. The reaction of **16** having the tosyl group gave some unidentified compounds, and no dimerization proceeded.

Scheme 3



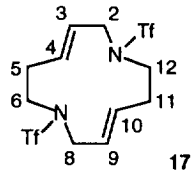
15 R = Tf
16 R = Ts

17 R = Tf 95 %
R = Ts 0 %

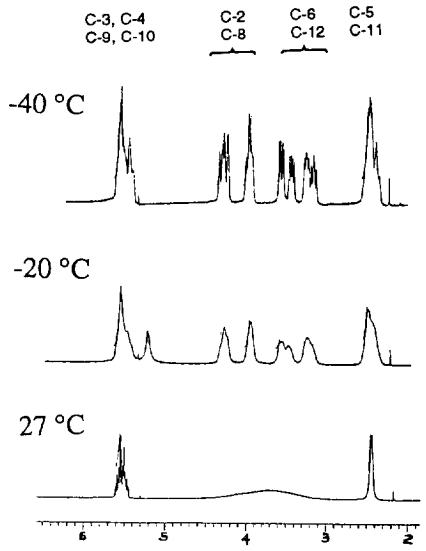
The ^{1}H-NMR study of **17** in $CDCl_3$ at various temperatures revealed the occurrence of the rapid change of the conformation at room temperature. The methylene signals on C-2, C-6, C-8 and C-12 carbons (for numbering see the formula of **17** in Figure 1) appeared as separate resonances below -40°C. Raising the temperature to -20 °C caused broadening of all the signals. At 27 °C the methylene signals collapsed to a broad resonance centered at δ 3.7. The results suggest the fluxional behavior of **17** at the higher temperature.

Figure 1

^{1}H-NMR spectra (400 MHz) of **17**.

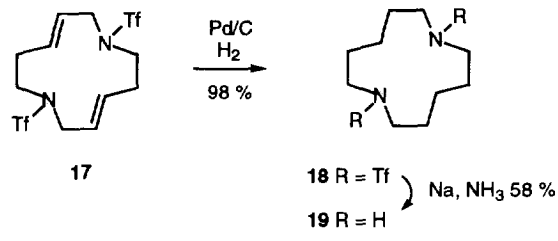


17



The cyclic dimer **17** was converted into 1,7-diazacyclododecane (**19**) by hydrogenation of the double bonds followed by desulfonylation. Polyazamacrocycles have recently attracted considerable interest as ligands and clathrate compounds, and some procedures to prepare polyazamacrocycles have been reported. However, most of the methods employ the Richman and Atkins' synthesis and its improvements[3], and generally, yields of those reactions were not very high. The present palladium-catalyzed synthesis does not require the high-dilution method, thus providing a new, convenient route to the unsaturated diaza macrocycles.

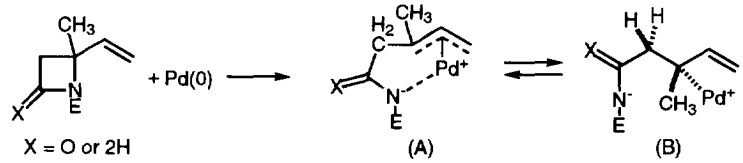
Scheme 4



Discussion

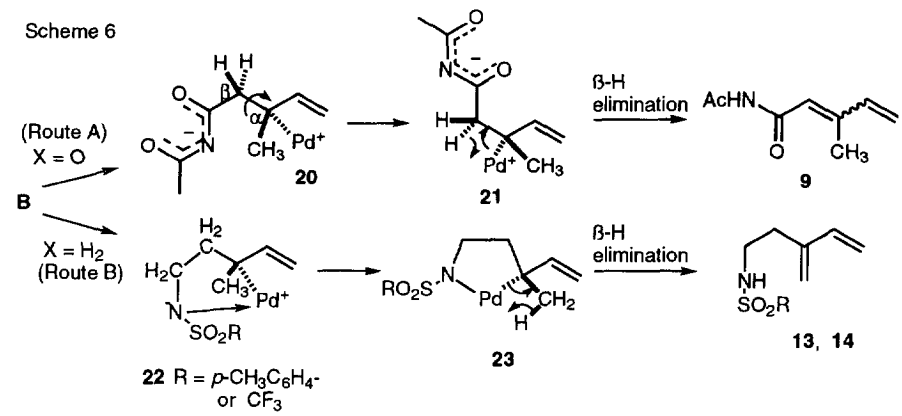
The azetidinones and azetidines having the vinyl substituent attached to a strained small ring are susceptible to ring opening in the presence of a palladium catalyst, similarly to other small ring compounds with unsaturated groups[4]. The driving force for the palladium-catalyzed ring opening is probably the release of the strain in the small ring with formation of a π-allylpalladium intermediate (A). The π-σ conversion

Scheme 5



gives a σ-allylpalladium complex (B), from which there are two alternative routes for the subsequent β-hydrogen elimination to afford the diene products. The vinylazetidinones, **5** and **6**, having acidic hydrogens adjacent to the amide carbonyl group are susceptible to the hydrogen abstraction to give the 2,4-pentadienylamide **9** and **10**. On the other hand, in the reaction of the vinylazetidines without the carbonyl group (**11** and **12**), the β-hydrogen abstraction predominantly took place at the methyl substituent to liberate the aminodienes with the exomethylene entity (**13** and **14**). In the latter case, a possible participation of the amido anion to form an amido-palladium bond[5] may be involved. When the five-membered ring[6] such as **22** is formed, the exclusive β-hydrogen elimination from the methyl group as shown in **23** will follow. The subsequent transfer of the hydride to the nitrogen gives the dienes **13** and **14** (Route B).

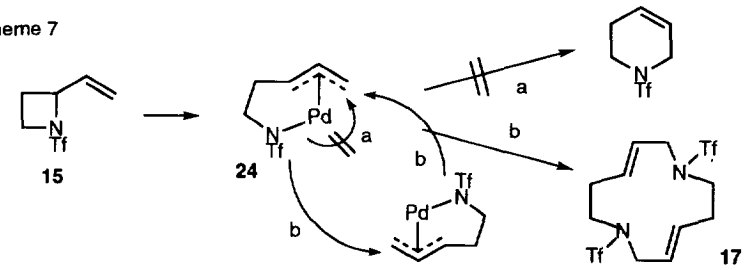
Scheme 6



In the former case (Route A) the bonding interaction between the nitrogen and the palladium may not be so strong probably because a negative charge on the nitrogen atom is delocalized by conjugating to the carbonyl groups. Thus, the rotation around the CH_2-C(α) bond in **20** may be possible to allow the β-hydrogen elimination from the β-methylene group in **21** to produce the linear pentadienoic amides, **9** and **10**. The result suggests usefulness of the present method for selective diene synthesis.

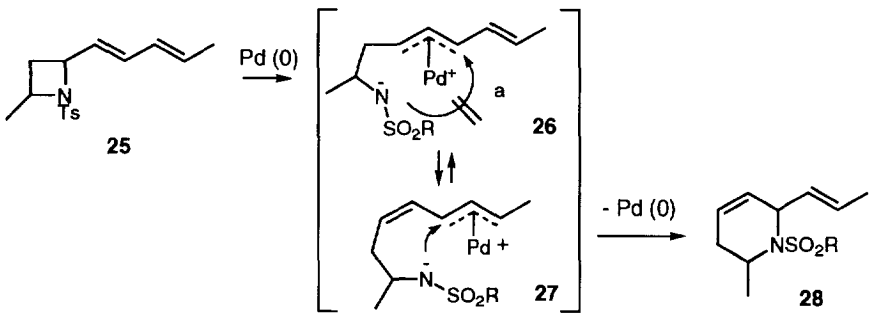
For the vinylazetidine **15** without the methyl group, no route is provided for the β-hydrogen abstraction as we discussed for the route B in Scheme 6. Thus, the amide group in **24** is considered to be led to attack at the less-substituted terminal of the neighboring π-allylpalladium complex through route b to form the macrocyclic dimer **17** as follows.

Scheme 7



No formation of piperidine was observed in the reaction of **15**, whereas transformation of dienyl azetidine **25** to piperidine **28** with palladium catalyst is known[2a]. The difference may arise from the unfavorable mutual configuration of the amide group with the less substituted terminal of the π-allyl intermediate **24** for the internal attack through route a [7]. In the case of the reaction of **25**, π-allylpalladium intermediate **26** may isomerize to **27**, which is possible to cyclize to the piperidine in an exocyclic mode.

Scheme 8



R = *p*-$CH_3C_6H_4$-

In conclusion, the present study demonstrates that the reaction course in the ring opening reactions of vinyl substituted four-membered azacycles is determined by the nature of the substrates. Assumption of formation of π-allylpalladium intermediates having a nitrogen atom with differing bonding abilities with cationic palladium center provides reasonable explanation for the formation of considerably varied reaction products, **2**, **3**, and **4**.

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Experimental

General methods. All melting points were measured on a Yanaco melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a JEOL GSX-400 (400 MHz), EX-270 (270 MHz) or a HITACHI R-90 (90 MHz) instrument. Chemical shifts are reported in parts per million downfield from internal Me_4Si (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broadened). ^{13}C NMR spectra were recorded on a JEOL GSX-400 (100 MHz), EX-270 (67.9 MHz) or a HITACHI R-90 (22.5 MHz) instrument. Spectra are referenced to $CDCl_3$ (77.00 ppm). Infrared spectra (IR) were recorded on a Perkin-Elmer 1640 FT-IR spectrometer. Band frequencies are reported in cm^{-1}. Mass spectra were recorded on a JEOL JMS-AUTOMASS mass spectrometer combination-gas chromatography. High-resolution mass spectra (HRMS) were recorded on a JEOL JMS-SX102A. Elemental analysis was performed by Perkin Elmer PE2400II. Ether and THF were distilled from benzophenone ketyl. Dichloromethane was distilled on P_2O_5. DMSO and DMF were distilled on CaH_2. Thin layer chromatography (TLC) was performed using Merck silica gel 60F (Art. 5554). Chromatography was performed using Wakogel C-200 or C-300.

1-Acetyl-4-methyl-4-vinyl-2-azetidinone (**5**)

To a cold (-40 °C), stirred solution of acetyl chloride (1.60 mL, 22.5 mmol) and 2,6-lutidine (2.62 mL, 22.5 mmol) in CH_2Cl_2 (10 mL) was added 4-methyl-4-vinyl-2-azetidinone[1] (500 mg, 4.50 mmol) in small portions. The mixture was stirred for 1h at 20°C. The resulting mixture was washed with 1N HCl, saturated aqueous $NaHCO_3$, and brine and then dried with $MgSO_4$ and concentrated. The residual oil was purified by chromatography on silica gel with hexane-EtOAc (9:1) as eluent to give **5** (502 mg, 73%) as a colorless oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.00 (dd, 1H, J = 10.0, 17.5 Hz), 5.12 (d, 1H, J = 10.0 Hz), 5.13 (d, 1H, J = 17.5 Hz), 2.85 (d, 1H, J = 17.5 Hz), 2.75 (d,1H, J = 17.5 Hz), 2.23 (s, 3H), 1.56 (s, 3H), IR (neat) 1786, 1701, 1375, 1306 cm^{-1}, MS *m/e* 157 (M$^+$); Anal. Calcd for $C_8H_{11}O_2N$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.95; H, 7.43; N, 9.18.

1-Acetyl-4-vinyl-2-azetidinone (**6**)

According to similar procedure of synthesis of **5**, **6** was obtained (615 mg, 86%) from 4-vinyl-2-azetidinone[1] (500 mg, 5.15 mmol): ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.30-5.20 (m, 3H), 4.60-4.20 (m, 1H), 3.30 (dd, 1H, J = 6.0, 15.4 Hz), 2.90 (dd, 1H, J = 3.8, 15.4 Hz), 2.4 and 2.2 (s, 3H), IR (neat) 1788, 1707, 1375, 1309 cm^{-1}, MS *m/e* 139 (M$^+$); Anal. Calcd for $C_7H_9O_2N$: C, 60.42; H, 6.52; N, 10.07. Found: C, 59.99; H, 6.62; N, 9.58.

1-Benzyl-4-methyl-4-vinyl-2-azetidinone (**8**)

To an ice-cooled, stirred suspension of benyl bromide (3.3 mL, 27.5 mmol) and potassium hydroxide (1.54 g, 30 mmol) and tetrabutylammonium sulfonium hydrate (0.86 g, 2.5 mmol) in THF (30 mL), was added 4-methyl-4-vinyl-2-azetidinone (2.78 g, 25 mmol) in small portion. After being stirred at rt for 5 h under Ar, the reaction was quenched with saturated aqueous ammonium chloride (300 mL). The mixture was extracted with ether (3*50 mL) and the extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residual oil was purified by chromatography on silica gel with hexane-EtOAc (3:2) as an eluent to give **8** (4.37 g, 87%) as a colorless oil; ^{1}H-NMR (90MHz, $CDCl_3$) δ 1.29 (s, 3H), 2.86 (s, 3H), 4.27 (dd, 2H, J = 15.3, 16.8Hz), 5.07 (dd, 1H, J = 3.6, 10.0Hz), 5.23 (d, 1H, J = 3.1Hz), 5.81 (dd, 1H, J = 10.3, 18.0 Hz), 7.2-7.4 (m, 5H); ^{13}C NMR (67.9MHz, $CDCl_3$) 165.6, 139.4, 136.4, 127.9, 127.8, 126.8, 115.5, 57.6, 50.2, 43.0, 20.8; IR ($CHCl_3$) 3480, 3080, 3010, 2930, 1745, 1395 cm^{-1}; MS m/e 201; Anal. calcd for $C_{13}H_{15}NO$: C; 77.58, H; 7.51,N; 6.96, Found C; 77.54, H; 7.82, N; 6.90.

N-Acetyl-3-methyl-2,4-pentadienamide (**9**)

To a mixture of $Pd_2(dba)_3CHCl_3$ (9 mg, 0.01 mmol) and *n*-Bu_3P (9 μL, 0.04 mmol) in DMSO (3 mL) was added **5** (55 mg, 0.359 mmol). The mixture was heated at 120 °C for 3 h. After being cooled to room temperature, water (5 mL) was added. The organic layer was extracted with CH_2Cl_2 (3 × 4 mL), dried with $MgSO_4$, and concentrated in vacuo. The residual oil was purified by chromatography on silica gel with hexane-EtOAc (7:3) as eluent to give **9** (*E*:*Z* = 1:1 mixture) (48 mg, 88%) as a white solid: ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.50 (br, 2H), 7.76 (dd, 1H, J = 10.8, 17.3 Hz), 6.45 (dd, 1H, J = 10.8, 17.3 Hz), 6.09 (s, 1H), 5.99 (s, 1H), 5.69 (d, 1H, J = 17.3 Hz), 5.67 (d, 1H, J = 17.3 Hz), 5.51 (d, 1H, J = 10.8 Hz), 5.47 (d, 1H, J = 10.8 Hz), 2.42 (s, 6H), 2.33 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 173.3, 173.2, 165.9, 165.1, 153.5, 152.1, 139.9, 133.9, 121.1, 121.0, 119.8, 119.2, 25.0 (2 carbons), 20.5, 13.4; mp 70-72 °C; IR (KBr) 3253, 1719, 1693, 1603, 1496, 1377, 1304, 1144 cm^{-1}; Anal. Calcd for $C_8H_{11}O_2N$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.81; H, 7.10; N, 9.18.

(E)-N-Acetyl-2,4-pentadienamide (**10**)

According to similar procedure of synthesis of **9**, **10** was obtained (37 mg, 74%) from **6** (50 mg, 0.36 mmol): ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.60 (br, 1H), 7.40 (dd, 1H, J = 11.0, 15.0 Hz), 6.52 (ddd, 1H, J = 10.0, 11.0, 16.9 Hz), 6.34 (d, 1H, J = 15.0 Hz), 5.69 (dd, 1H, J = 0.7, 16.9 Hz), 5.59 (dd, 1H, J = 0.7, 10.0 Hz), 2.42 (s, 3H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 172.8, 165.3, 145.8, 134.5, 127.1, 123.2, 25.2; mp 107-109 °C; IR (KBr) 3258, 1728, 1666, 1505, 1377, 1330, 1303, 1264, 1136 cm^{-1}; Anal. Calcd for $C_7H_9O_2N$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.21; H, 6.39; N, 9.54.

N-Tosyl-2-methyl-2-vinylazetidine (**11**)

To a solution of 2-methyl-2-vinylazetidine (100 mg, 1.03 mmol) and Et_3N (0.42 mL, 3.0 mmol) in CH_2Cl_2 (10 mL) was added *p*-toluenesulfonyl chloride (196 mg, 1.03 mmol) at 0 °C. The mixture was stirred for 15 min at rt. Water (2 mL) was added to the mixture, and the resulting was extracted with CH_2Cl_2 (3×5 mL). The combined extracts were dried with $MgSO_4$ and concentrated. The residual oil was purified by chromatography on silica gel with hexane-EtOAc (17:3) as eluent to give **11** (180 mg, 70%) as a colorless oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.78 (d, 2H, J = 7.9 Hz), 7.30 (d, 2H, J = 7.9 Hz), 6.13 (dd, 1H, J = 9.5, 15.5 Hz), 5.29 (dd, 1H, J = 1.6, 15.5 Hz), 5.13 (dd, 1H, J = 1.6, 9.5 Hz), 4.00-3.55 (m, 2H), 2.50 (s, 3H), 2.40-1.98 (m, 2H), 1.65 (s, 3H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 143.2, 141.1, 136.8, 129.4, 127.7, 113.9, 73.0, 45.4, 30.1, 24.4, 21.5; IR (neat) 1338, 1157, 1096, 996, 680 cm^{-1}; Anal. Calcd for C13H17O2NS: C, 62.12; H, 6.82; N, 5.57. Found: C, 62.25; H, 7.01; N, 5.58.

N-Trifluoromethanesulfonyl-2-methyl-2-vinylazetidine (**12**)

To a solution of 2-methyl-2-vinylazetidine (100 mg, 1.03 mmol) in THF (5 mL) was added dropwise *n*-BuLi (0.62 mL of a 1.65 M solution in hexane, 1.03 mmol) at -30 °C under Ar. After the mixture was stirred at the same temperature for 15 min, a solution of N-phenyltrifluoromethanesulfonimide (367 mg, 1.03 mmol) in THF (2 mL) was added to the above solution at -40 °C. After stirring for 1.5 h, the mixture was stirred at 0 °C for an addition 1 h. Water (5 mL) was added to the mixture, and the resulting was extracted with Et_2O (3×5 mL). The combined extracts were dried ($MgSO_4$) and concentrated. The residual oil was purified by chromatography on silica gel with hexane-EtOAc (19:1) as eluent to give **12** (81 mg, 34%) as a colorless oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.23 (dd, 1H, J = 10.5, 17.5 Hz), 5.26 (d, 1H, J = 17.5 Hz), 5.23 (d, 1H, J = 10.5 Hz), 4.15 (t, 2H, J = 7.5 Hz), 2.65-2.00 (m, 2H), 1.70 (s, 3H); ^{13}C NMR (67.9 MHz, $CDCl_3$)[8] δ 139.8, 115.0, 65.0, 47.1, 30.2, 25.4; ^{19}F NMR (254.2 MHz) δ -77.76; IR (neat) 1386, 1202, 1110 cm^{-1}; MS *m/e* 229 (M^+), 214

(M^+ -CH_3), 96 (M^+ -Tf); HRMS: calcd for $C_7H_{10}O_2NF_3S$ 229.03845, found 229.0419.

3-Methylene-5-(*N*-tosylamino)-1-pentene (**13**)
To a mixture of $Pd_2(dba)_3CHCl_3$ (5 mg, 0.005 mmol) and Ph_3P (11 mg, 0.04 mmol) in THF (1 mL) was added **11** (51 mg, 0.20 mmol) in THF (1 mL). The mixture was stirred at rt for 3 h. The resulting mixture was concentrated in vacuo. The residual oil was purified by chromatography on silica gel with hexane-EtOAc (19:1). Further purification by distillation under reduced pressure (5 mmHg, 100 °C) gave **13** (40 mg, 77%) as a colorless oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.78 (d, 2H, J = 8.5 Hz), 7.31 (d, 2H, J = 8.5 Hz), 6.30 (dd, 1H, J = 10.5, 17.7 Hz), 5.28-4.88 (m, 4H), 4.80-4.55 (m, 1H), 3.14 (dt, 2H, J = 7.0, 7.0 Hz), 2.42 (s, 3H), 2.38 (t, 2H, J = 7.0 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 143.3, 142.2, 137.7, 129.7, 127.1, 127.0, 118.0, 114.0, 41.4, 31.5, 21.5; IR (neat) 3284, 1597, 1422, 1326, 1158, 1095 cm^{-1}; Anal. Calcd for $C_{13}H_{17}O_2NS$: C, 62.12; H, 6.82; N, 5.57. Found: C, 62.0; H, 6.96; N, 5.58.

3-Methylene-5-(*N*-trifluoromethanesulfonylamino)-1-pentene (**14**)
According to the procedure of synthesis of **13**, a reaction of **12** (46 mg, 0.20 mmol) was carried out. Purification by chromatography on silica gel with hexane-EtOAc (9:1) gave **14** (35 mg, 77 %) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.31 (dd, 1H, J = 11.0, 18.2 Hz), 5.16 (d, 1H, J = 18.2 Hz), 5.13 (s, 1H), 5.10 (d, 1H, J = 11.0 Hz), 5.03 (s, 1H), 4.81 (br, 1H), 3.38 (q, 2H, J = 6.8 Hz), 2.48 (t, 2H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 137.4, 121.2 & 118.0 (central peaks of q, CF_3, J_{CF} = 320 Hz), 118.9, 114.6, 42.6, 32.3; ^{19}F NMR (254.2 MHz) δ -78.11; IR (neat) 3316 (N-H), 1597, 1372, 1192, 905 cm^{-1}, MS *m/e* 229 (M^+), 96 (M^+ -Tf); Anal. Calcd for $C_7H_{10}O_2NSF_3$: C, 36.68; H, 4.40; N, 6.11. Found: C, 36.76; H, 4.56; N, 6.10.

2-Vinylazetidine
According to similar procedure in Hassner's report[1c], reduction was carried out: to a stirred, ice cold suspension of $LiAlH_4$ (6.24 g, 164 mmol) in ether (200 mL) under argon was added dropwise sulfuric acid (8.50 g, 82.0 mmol). After stirring for an additional hour, 4-vinyl-2-azetidinone (6.00 g, 62.0 mmol) was added dropwise, and the mixture was refluxed for 3 days. To the resulting mixture was added water (12 mL), and the mixture was stirred for 1 h. The solid was removed by filtration. The filtrate was distilled to give 2-vinylazetidine (1.06 g) as a colorless oil containing a small amount of ether (35 mmHg, 35 °C). It was used in next operation without further purification: ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.11 (ddd, 1H, J = 6.5, 10.0, 17.3 Hz), 5.10 (dt, 1H, J = 1.2, 17.3 Hz), 5.04 (dt, 1H, J = 1.2, 10.0 Hz), 4.35 (q, 1H, J = 6.5 Hz), 3.75-3.23 (m, 2H), 2.60-1.98 (m, 2H), 2.05 (s, 1H).

N-Trifluoromethanesulfonyl-2-vinylazetidine (**15**)
According to the procedure of synthesis of **12**, a reaction of 2-vinylazetidine (1.0 g, 12.0 mmol) was carried out to give **15** (878 mg, 34%) as a colorless oil: ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.01 (ddd, 1H, J = 7.4, 9.9, 17.0 Hz), 5.34 (dt, 1H, J = 1.0, 17.0 Hz), 5.29 (dt, 1H, J = 1.0, 9.9 Hz), 5.05 (dt, 1H, J = 7.4, 15.3 Hz), 4.25 (dt, 1H, J = 8.2, 16.6 Hz), 3.98 (dt, 1H, J = 4.6, 8.2 Hz), 2.62-2.50 (m, 1H), 2.33-2.17 (m, 1H); ^{13}C NMR (67.9 MHz, $CDCl_3$)[8] δ 135.9, 119.1, 67.0, 49.1, 22.9; ^{19}F NMR (254.2 MHz) δ -76.1; IR (neat) 1383, 1192, 1098 cm^{-1}, MS *m/e* 215 (M^+); HRMS: calcd for $C_6H_8O_2NF_3S$ 215.0228, found 215.0258.

N-Tosyl-2-vinylazetidine (**16**)
According to the procedure of synthesis of **11**, a reaction of 2-vinylazetidine (300 mg, 3.6 mmol) was carried out to give **16** (400 mg, 47%) as a colorless oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.68 (d, 2H, J = 8.0 Hz), 7.32 (d, 2H, J = 8.0 Hz), 5.95 (ddd, 1H, J = 6.5, 10.0, 17.0 Hz), 5.23 (d, 1H, J = 17.0 Hz), 5.15 (d, 1H, J = 10.0 Hz), 4.27 (q, 1H, J = 6.5 Hz), 3.70-3.37 (m, 2H), 2.40 (s, 3H), 2.19-1.85 (m, 2H).

1,7-Ditrifluoromethanesulfonyl-1,7-diazacyclododeca-4, 10-diene (**17**)
According to the procedure of synthesis of **13**, a reaction of **15** (200 mg, 0.93 mmol) was carried out at 0 °C. Purification by chromatography on silica gel with hexane-EtOAc (9:1) and recrystallization (ether) gave **17** (190 mg, 95%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 5.57 (dt, 2H, J = 6.6, 15.6 Hz), 5.49 (dt, 2H, J = 5.5, 15.6 Hz), 4.50-3.00 (br, 8H), 2.44 (m, 4H); ^{1}H NMR (400 MHz, $CDCl_3$, -40 °C) δ 5.65-5.40 (m, 4H), 4.30 (dd, 2H, J = 16.2, 27.9 Hz), 4.04-3.92 (m, 2H), 3.69 (dd, 1H, J = 7.3, 16.1 Hz), 3.45 (dd, 1H, J = 8.8, 16.1 Hz), 3.28 (m, 1H) 3.20 (m, 1H), 2.58-2.34 (m, 4H); ^{13}C NMR (100.4 MHz, $CDCl_3$, 25°C) δ 133.3, 128.4, 122.0 & 118.7 (central peaks of q, CF_3, J_{CF} = 330 Hz), 53.2, 52.0, 33.0; ^{19}F NMR (254.2 MHz) δ -74.3; mp 129-130 °C; IR ($CHCl_3$) 3015, 1390, 1195 cm^{-1}; MS *m/e* 430 (M^+), 297 (M^+ -Tf), 215 ($TfNCH_2CHCHCH_2CH_2$); HRMS: calcd for $C_{12}H_{16}F_6N_2O_4S_2$ 430.0457, found 430.0484, Anal. Calcd. C; 33.49, H; 3.75, N; 6.51, Found C; 33.69, H; 3.72, N; 6.46.

1,7-Ditrifluoromethanesulfonyl-1,7-diazacyclododecane (**18**)
To a solution of **17** (150 mg, 0.35 mmol) in EtOH (15 mL) and CH_2Cl_2 (15 mL) was added 10% Pd/C (10 wt%, 75 mg), and the resulting suspension was vigorously stirred under 1 atm of H_2 for 20 h. After removal of the catalyst by filtration, the filtrate was concentrated. Recrystallization in ether gave **18** (147 mg, 98 %) as a white solid; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.55-3.28 (br, 8H), 1.85-1.54 (m, 12H); ^{13}C NMR (67.9 MHz, $CDCl_3$)[8] δ 49.7, 26.7, 21.1; ^{19}F NMR (254.2 MHz) δ -69.9; IR (KBr) 1378, 1220, 1146 cm^{-1}, m.p. 167-169 °C; Anal. Calcd for $C_{12}H_{20}O_4N_2F_6S_2$: C, 33.18; H, 4.64; N, 6.45. Found: C, 33.43; H, 4.46; N, 6.17.

1,7-Diazacyclododecane (**19**)
To a mixture of liquid NH_3 (9 mL) and THF (1 mL) was added Na (50 mg) at -40 °C. The color turned blue. To the mixture was added **18** (140 mg, 0.322 mmol) in THF (5 mL), and the resulting mixture was stirred for 1 h. The reaction was quenched with methanol (5 mL). The mixture was allowed to warm to room temperature, and concentrated in vacuo. To the residue was added 6N-NaOH (2 mL), and organic layer was extracted with AcOEt (4×5 mL). The combined extracts were dried with $MgSO_4$ and concentrated. The residual oil was washed with ether, and concentrated to give **19** (32 mg, 58%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.90 (br, 2H), 2.67-2.56 (m, 8H), 1.65-1.42 (m, 12H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 47.0, 26.1, 20.8; IR (neat) 3266, 2932, 1448 cm^{-1}; HRMS (FAB): calcd for $C_{10}H_{22}N_2$ 170.17835, found 171.1840 $(M+1)^+$.

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8. The ^{13}C NMR signal of CF_3 (quartet) was unable to be observed in this measurement because of its low intensity.

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