Intermolecular Addition of Amines to an *N*-Tosyloxy *β*-Lactam[1]

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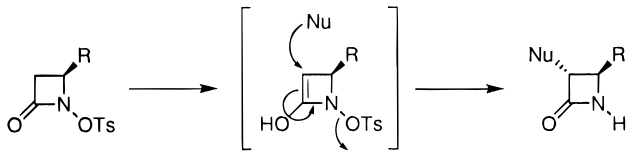
The emergence of resistance by bacteria to many of the currently used *β*-lactam antibiotics has led to the search for new and improved antibiotics.[2] One area of interest in our research group is the development of new methods to selectively functionalize the *β*-lactam ring. We have recently reported the discovery of a remarkable reaction for the addition of nucleophiles to the C-3 position of *N*-tosyloxy *β*-lactams (Scheme 1).[3] Treatment of a variety of *N*-tosyloxy *β*-lactams with a tertiary amine base in the presence of various nucleophiles including azide, chloride, bromide, iodide, acetate, and others afforded products in which the nucleophile had added to the C-3 position of the *β*-lactam and the N−O bond had been cleaved. The addition proceeded with predominately *trans* stereochemistry relative to the substituent at C-4. Presumably, this transformation occurred by a base-catalyzed enolization followed by an S_N2' displacement of the tosylate during attack of the nucleophile on the enol intermediate. Hoffman and co-workers have recently described a similar transformation on acyclic hydroxamate systems.[4]

One class of nucleophiles which we had not yet fully explored was amine nucleophiles. The addition of amines to the C-3 position of *N*-tosyloxy *β*-lactams would allow for the facile introduction of the α-amino substituent on the *β*-lactam ring and therefore provide a useful route to important α-amino *β*-lactam derivatives. In some of our previous work we showed that tertiary amines such as triethylamine and diisopropylethylamine (Hünig's base) added competitively with some of the nucleophiles used in the nucleophilic addition reaction.[3] By using primary and secondary amines, we anticipated that the amine would serve as both the catalyst and the nucleophile to provide precursors to biologically interesting α-amino *β*-lactams.

For this study we chose *β*-lactam **1** as our substrate. The synthesis of *β*-lactam **1** from the corresponding commercially available *β*-hydroxy ester by our hydroxamate-mediated approach[5] was straightforward and has been reported.[3b] To avoid competitive attack of the nucleophilic amines at the *β*-lactam carbonyl, we first studied reactions with sterically hindered amines. Thus, treatment of *β*-lactam **1** with 2 equiv of diisopropylamine afforded addition to the C-3 position of *β*-lactam **1** in excellent overall yield (Table 1). The addition of another relatively hindered amine, *tert*-butylamine, also afforded mostly the anticipated C-3 addition products **2b** (major) and **3b** (minor) as well as small amounts of amide **4b**.

Scheme 1



The proposed mechanism for the formation of amide **4b** is shown in Scheme 2 (R^1 = *t*-Bu, R^2 = H). First the amine apparently attacked the *β*-lactam carbonyl opening the ring to afford hydroxylamine **5**. Elimination of a molecule of *p*-toluenesulfonic acid from **5** afforded imine **6** which then hydrolyzed to give the observed product **4**.

Interestingly, substitution of isopropylamine for diisopropylamine or *tert*-butylamine completely altered the course of the reaction. Thus, treatment of *β*-lactam **1** with 2 equiv of isopropylamine followed by ^{1}H NMR analysis of the crude reaction mixture showed that no addition of isopropylamine to the C-3 position had occurred. Instead, after purification, amide **4c** was isolated in good yield (82−89%), indicating that isopropylamine attacked *β*-lactam **1** only at the carbonyl carbon as shown in Scheme 2 (R^1 = *i*-Pr, R^2 = H). The addition of diethylamine also was tried since it is more hindered than isopropylamine but less hindered than diisopropylamine and *tert*-butylamine. Treatment of *β*-lactam **1** with 2 equiv of diethylamine afforded a 32% yield of addition to C-3.

Nucleophilic addition of ammonia or an ammonia equivalent at the C-3 position of various C-4-substituted *N*-tosyloxy *β*-lactams would provide a direct route to monobactam[6] precursors (Scheme 3). Subsequent acylation of the C-3 amine with physiologically appropriate side chains and standard introduction of the ring N−SO_3H linkage would allow production of a tremendous variety of monobactams and analogs. Current variation of substituents at the C-4 position of monobactams most often requires access to the corresponding *β*-hydroxy amino acid precursors **7**. While some naturally-occuring *β*-hydroxy amino acids, such as serine (**7**, R = H) and threonine (**7**, R = Me), are readily available, others are much less common or require total syntheses themselves.[7] Alternatively, optically pure *β*-hydroxy acids **10** are readily available by asymmetric enzymatic[8] and chemical[9] reductions. Their conversion to 4-substituted-*N*-hydroxy *β*-lactams **11** by standard protocol[5] followed by tosylation and subsequent reaction with an ammonia equivalent (**12** → **9**) may provide an effective route to an increased variety of monobactams **8**.

We previously demonstrated that azide is very effective in the C-3 nucleophile transfer reaction.[3b] While azides are readily reduced to amines, we also thought that it would be interesting to determine the compatibility of the C-3 nucleophile transfer process with other ammonia equivalents to avoid the generation and use of intermediate azides. One of our first considerations was that removal of the *tert*-butyl group from **2b** should afford the

(1) Results presented, in part, at the 29th Great Lakes Meeting of the American Chemical Society, Normal, IL, May 1996, Program and Abstracts, 131, and at the 210th National Meeting of the American Chemical Society, Chicago, IL, August 1995, Program and Abstracts, 358.

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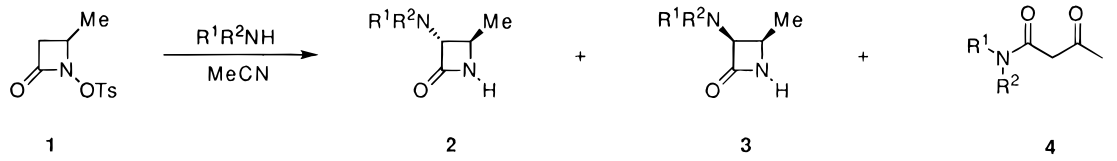
Table 1. Reactions of 1 with Amine Nucleophiles

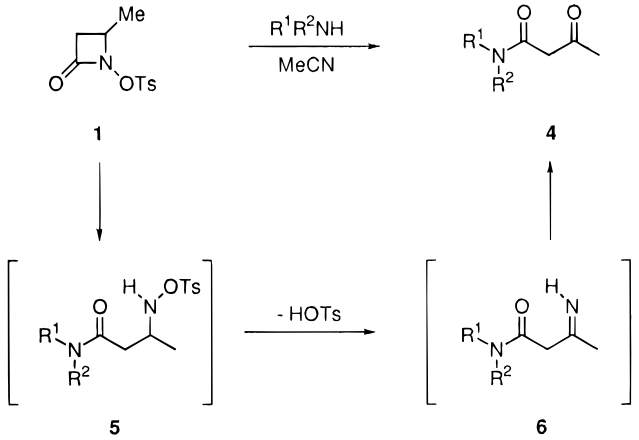


1 2 3 4

entry	R^1	R^2	**2** (%)[a]	**3** (%)[a]	**4** (%)[a]	pK_a	*i*-Pr_2NEt[d]
1	*i*-Pr	*i*-Pr	**2a** (86−88)	**3a** (5)	**4a** (0)	11.1[b]	no
2	*t*-Bu	H	**2b** (80−89)	**3b** (6−7)	**4b** (3−10)	10.5[b]	no
3	*i*-Pr	H	**2c** (0)	**3c** (0)	**4c** (82−89)	10.6[b]	no
4	Et	Et	**2d** (29−32)	**3d** (0)	**4d** (0)	11.0[b]	no
5	Ph_3C	H	**2e** (21−22)	**3e** (0)	**4e** (0)	6.1[c]	yes
6	Ph_2CH	H	**2f** (37−44)	**3f** (0)	**4f** (0)	7.2[c]	yes
7	allyl	allyl	**2g** (45−49)	**3g** (0)	**4g** (0)	9.3[b]	yes

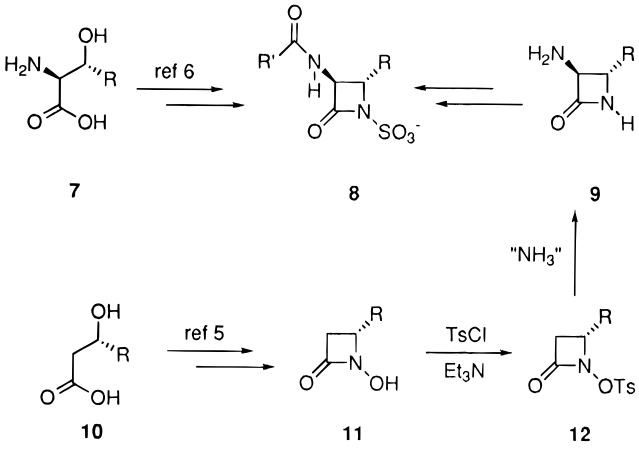
[a] Isolated yields after purification. [b] See ref 13. [c] Determined in methylcellosolve/water, see ref 11. [d] In some cases, *i*-Pr_2NEt was added to catalyze the enolization.

Scheme 2



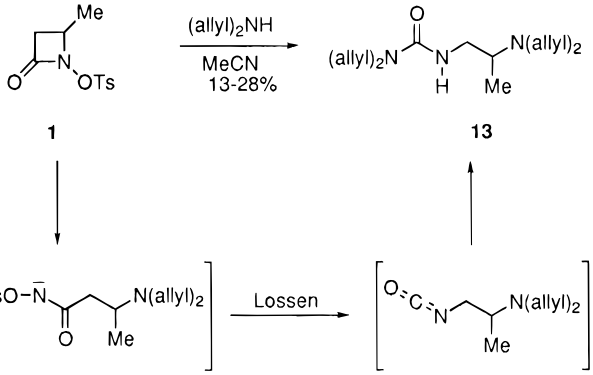
1 4 5 6

Scheme 3



7 8 9 10 11 12

Scheme 4



1 13 14 15

Treatment of β-lactam **1** with 2 equiv of tritylamine along with the addition of 2 equiv of diisopropylethylamine, to catalyze the apparently required enolization, led to addition of tritylamine to the C-3 position in 21−22% yield. Treatment of β-lactam **1** with 2 equiv of aminodiphenylmethane (pK_a = 7.2)[11] also afforded no addition to C-3; however, when diisopropylethylamine was added to the reaction the C-3 addition product **2f** was obtained in 37−44% yield.

The addition of diallylamine was attempted since rhodium-catalyzed isomerization of the allyl groups to imines followed by hydrolysis of the imines should afford the free amine.[12] Interestingly, treatment of β-lactam **1** with 2 equiv of diallylamine afforded urea **13** in 24% yield. Only a small amount (<10%) of the desired C-3-substituted β-lactam **2g** was isolated. The presumed pathway for the formation of urea **13** is shown in Scheme 4. Apparently attack of diallylamine in an S_N2 fashion at the C-4 carbon of β-lactam **1** opened the ring to form hydroxamate anion **14** which then initiated a facile Lossen rearrangement to isocyanate **15**. Isocyanate **15** was then trapped by another molecule of diallylamine to give the observed product **13**. Diallylamine may not be basic enough (pK_a = 9.3)[13] to sufficiently catalyze the proposed enolization, thus allowing for other chemistry, such as the observed attack at C-4, to take place. When the reaction was repeated using 3 equiv of diisopropylethylamine and 1.6 equiv of diallylamine, the C-3 addition product **2g** was obtained in 45−49% yield along with 13−15% of **13**.

free amine. However, our attempts to remove the *tert*-butyl group from **2b** have so far been unsuccessful. Since the trityl group can be deprotected under relatively mild conditions,[10] we attempted to add tritylamine to the C-3 position of β-lactam **1**. Treatment of β-lactam **1** with 2 equiv of tritylamine afforded only recovery of starting material. Apparently, tritylamine (pK_a = 6.1)[11] is not basic enough to catalyze the proposed enolization. It appears as though the pK_a of the amine needs to be approximately 11 to efficiently catalyze the enolization.

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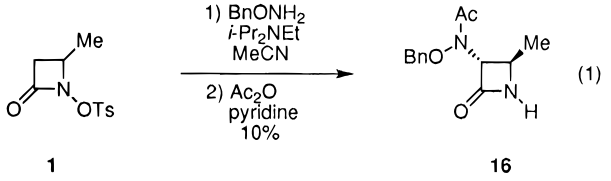
Compound **2g** after deprotection represents a formal synthesis of the monobactams.

Hydroxylamines are effective nucleophiles despite their reduced basicity relative to ammonia or alkylamines. N−O-reduction also affords amines from hydroxylamines. Thus, the addition of an O-protected hydroxylamine to the C-3 position of *N*-tosyloxy *β*-lactams was anticipated to give the desired monobactam precursors after N−O-reduction; also, retention of the N−O bond would provide access to novel structural types and complement our interest in hydroxamate-substituted *β*-lactam antibiotics.[14] Treatment of *β*-lactam **1** with 2 equiv of *O*-benzylhydroxylamine resulted in no observed addition to C-3. Most of the starting material was recovered. Analogous to the addition of tritylamine, aminodiphenylmethane, and diallylamine, *O*-benzylhydroxylamine ($pK_a = 4.3$)[15] apparently is not basic enough to catalyze the proposed enolization. Treatment of *β*-lactam **1** with 1.6 equiv of *O*-benzylhydroxylamine and 3 equiv of diisopropylethylamine led to addition at C-3. However, the product appeared to decompose over time. To help prevent this decomposition, the hydroxylamine was acylated (Ac_2O, pyridine) and *β*-lactam **16** was isolated in 10% yield (eq 1).



1 **16**

In summary, we have shown that *N*-tosyloxy *β*-lactams are highly reactive molecules. Nucleophilic attack by amines on the *β*-lactam ring can occur at all three carbon atoms of the *β*-lactam ring. The position where the amine attacks the *β*-lactam ring appears to depend largely on the basicity and steric hinderance of the amine nucleophile. Apparently, the pK_a of the amine nucleophile needs to be approximately 11 to efficiently promote attack at C-3. If the pK_a of the amine is not basic enough, other more basic non-nucleophilic amines need to be added to the reaction to apparently promote prior enolization. Control of nucleophile transfer to the C-3 position of *β*-lactams promises to considerably enhance the chemistry of this very important class of compounds. The alternate reactivity demonstrated in these reactions also may lead to new considerations in the design of therapeutic agents. For example, we have recently demonstrated use of *N*-(arylsulfonyl)oxy *β*-lactams as electrophilic "bombs" as novel and potent *β*-lactamase inhibitors.[16]

Experimental Section

General Methods. Instruments and general methods used have been described previously.[3b]

(±)-*trans*-3-(*N*,*N*-Bis(1-methylethyl)amino)-4-methyl-2-azetidinone (2a) and (±)-*cis*-3-(*N*,*N*-Bis(1-methylethyl)-amino)-4-methyl-2-azetidnone (3a). To a stirred solution of 30 mg (0.12 mmol) of *β*-lactam **1** in 1.0 mL of anhydrous MeCN at rt under N_2 was added 35 *μ*L (0.25 mmol) of diisopropylamine. After the solution was stirred for 44 h at rt, the solvent was evaporated to afford a white solid. The solid was chromatographed on silica gel eluting with 30% EtOAc in hexanes to afford 19 mg (86%) of **2a** as a white solid and 1 mg (5%) of **3a** as a colorless oil. An analytical sample of **2a** was obtained by recrystallization from hexanes: mp 104−106 °C; R_f 0.24 (2:3 EtOAc:hexanes); IR ($CHCl_3$) 3435, 1745 (CO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *δ* 1.03 (d, $J = 6.7$ Hz, 6H), 1.11 (d, $J = 6.6$ Hz, 6H), 1.33 (d, $J = 6.0$ Hz, 3H), 3.11 (heptet, $J = 6.6$ Hz, 2H), 3.57 (qd, $J = 6.1$, 2.2 Hz, 1H,), 3.77 (d, $J = 2.2$ Hz, 1H), 6.04 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 18.88, 22.29, 23.25, 46.10, 52.57, 72.57, 172.56; HRMS (FAB) calcd for $C_{10}H_{21}N_2O$ (MH^+) 185.1654, found 185.1652. Anal. Calcd for $C_{10}H_{20}N_2O$: C, 65.18; H, 10.94; N, 15.20. Found: C, 65.40; H, 10.70; N, 15.29. Compound **3a**: R_f 0.34 (2:3 EtOAc:hexanes); IR ($CHCl_3$) 3420, 1745 (CO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) *δ* 1.03 (d, $J = 6.5$ Hz, 6H), 1.15 (d, $J = 6.5$ Hz, 6H), 1.23 (d, $J = 6.5$ Hz, 3H), 3.13 (heptet, $J = 6.5$ Hz, 2H), 3.62−3.69 (m, 1H), 4.42 (dd, $J = 5.0$, 1.5 Hz, 1H), 5.80 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 16.68, 21.85, 23.45, 47.76, 52.69, 67.80, 172.32; HRMS (FAB) calcd for $C_{10}H_{21}N_2O$ (MH^+) 185.1654, found 185.1651.

(±)-*trans*-3-(*N*-(1,1-Dimethylethyl)amino)-4-methyl-2-azetidinone (2b), (±)-*cis*-3-(*N*-(1,1-dimethylethyl)amino)-4-methyl-2-azetidinone (3b), and *N*-(1,1-Dimethylethyl)-3-oxobutanamide (4b). To a stirred solution of 58 mg (0.23 mmol) of *β*-lactam **1** in 2.0 mL of anhydrous MeCN at rt under N_2 was added 50 *μ*L (0.48 mmoL) of *tert*-butylamine. After the solution was stirred for 47 h at rt, the white precipitate which had formed was filtered off and the filtrate was concentrated to afford a yellow solid. The yellow solid was chromatographed on silica gel eluting with EtOAc to afford 31 mg (89%) of **2b** as a white solid, 2 mg (6%) of **3b** as a light yellow oil, and 1 mg (3%) of **4b** as a white solid. An analytical sample of **2b** was obtained by recrystallization from hexanes: mp 117−119 °C; R_f 0.15 (EtOAc); IR (KBr) 3270, 1750 (CO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *δ* 1.12 (s, 9H), 1.37 (d, $J = 6.1$ Hz, 3H), 1.78 (br s, 1H), 3.43 (qd, $J = 6.1$, 1.7 Hz), 3.71 (s, 1H), 6.09 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 19.04, 29.61, 50.51, 56.65, 68.70, 170.06; HRMS (FAB) calcd for $C_8H_{17}N_2O$ (MH^+) 157.1341, found 157.1339. Anal. Calcd for $C_8H_{16}N_2O$: C, 61.51; H, 10.32; N, 17.93. Found: C, 61.38; H, 10.15; N, 17.97. Compound **3b**: R_f 0.32 (EtOAc); IR ($CHCl_3$) 3420, 1755 (CO), cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *δ* 1.11 (s, 9H), 1.21 (d, $J = 6.3$ Hz, 3H), 1.55 (br s, 1H), 3.73−3.85 (m, 1H), 4.25 (dd, $J = 4.9$, 0.7 Hz), 5.90 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 16.39, 29.78, 50.39, 51.36, 63.46, 172.16; HRMS (FAB) calcd for $C_8H_{17}N_2O$ (MH^+) 157.1341, found 157.1304. Compound **4b**: mp 40−43 °C; R_f 0.50 (EtOAc); IR ($CHCl_3$) 3440, 3350, 1710 (CO), 1670 (CO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *δ* 1.36 (s, 9H), 2.26 (s, 3H), 3.33 (s, 2H), 6.69 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 28.64, 31.02, 50.87, 51.34, 164.40, 205.07; HRMS (FAB) calcd for $C_8H_{15}NO_2$ ($M^{+\bullet}$) 157.1103, found 157.1124.

***N*-(1-Methylethyl)-3-oxobutanamide (4c).** To a stirred solution of 34 mg (0.13 mmol) of *β*-lactam **1** in 1.0 mL of anhydrous MeCN at rt under N_2 was added 25 *μ*L (0.29 mmol) of isopropylamine. After the solution was stirred at rt for 14 h, the solvent was evaporated to afford a yellow oil. The oil was chromatographed on silica gel eluting with 80% EtOAc in hexanes to afford 17 mg (89%) of **4c** as a white solid. An analytical sample was obtained by recrystallization from hexanes: mp 51−53 °C; R_f 0.28 (4:1 EtOAc:hexanes); IR ($CHCl_3$) 3420, 3330, 1715 (CO), 1670 (CO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) *δ* 1.17 (d, $J = 6.5$ Hz, 6H), 2.27 (s, 3H), 3.38 (s, 2H), 4.02−4.14 (m, 1H), 6.74 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 22.56, 31.07, 41.46, 49.78, 164.40, 204.83; HRMS (FAB) calcd for $C_7H_{14}NO_2$ (MH^+) 144.1025, found 144.1023. Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.46; H, 8.91; N, 9.67.

(±)-*trans*-3-(*N*,*N*-Diethylamino)-4-methyl-2-azetidinone (2d). To a stirred solution of 41 mg (0.16 mmol) of *β*-lactam **1** in 1.1 mL of anhydrous MeCN at rt under N_2 was added 40 *μ*L (0.39 mmol) of diethylamine. After the solution was stirred at rt for 40 h, the solvent was evaporated to afford a brown solid. The solid was chromatographed on silica gel eluting with 80% EtOAc in hexanes to afford 8 mg (32%) of **2d** as a colorless oil: R_f 0.36 (9:1 EtOAc:hexanes); IR (neat) 3280, 1750 (CO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *δ* 1.07 (t, $J = 6.9$ Hz, 6H), 1.36 (d, $J = 6.3$ Hz, 3H), 2.62−2.84 (m, 4H) 3.66−3.78

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(m, 2H), 6.44 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.21, 19.64, 44.08, 49.50, 77.75, 169.32; HRMS (FAB) calcd for $C_8H_{17}N_2O$ (MH^+) 157.1341, found 157.1306.

(±)-*trans*-4-Methyl-3-[(triphenylmethyl)amino]-2-azetidinone (2e). To a stirred solution of 50 mg (0.20 mmol) of β-lactam **1** in 1.5 mL of anhydrous MeCN at rt under N_2 were added 110 mg (0.42 mmol) of tritylamine and 70 μL (0.40 mmol) of diisopropylethylamine. After 48 h of stirring under N_2, the solvent was evaporated and the residue was chromatographed on silica gel eluting with 30% EtOAc in hexanes to afford 14 mg (21%) of **2e** as a white solid. An analytical sample was obtained by recrystallization from EtOAc−hexanes: mp 183−185 °C; R_f 0.30 (2:3 EtOAc:hexanes); IR (KBr) 3220, 1755 (CO) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.38 (d, J = 6.0 Hz, 3H), 2.76 (br s, 1H), 3.02 (qd, J = 6.0, 1.5 Hz, 1H), 3.63 (br s, 1H), 5.96 (br s, 1H,), 7.16−7.54 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.48, 57.98, 70.00, 70.51, 126.64, 128.06, 128.77, 145.98, 170.43; HRMS (FAB) calcd for $C_{23}H_{22}N_2O$ ($M^{+\bullet}$) 342.1732, found 342.1743. Anal. Calcd for $C_{23}H_{22}N_2O$: C, 80.67; H, 6.48; N, 8.18. Found: C, 80.77; H, 6.70; N, 8.13.

(±)-*trans*-4-Methyl-3-[(diphenylmethyl)amino]-2-azetidinone (2f). To a stirred solution of 200 mg (0.783 mmol) of β-lactam **1** in 6.0 mL of anhydrous MeCN at rt under N_2 were added 410 μL (2.35 mmol) of diisopropylethylamine and 210 μL (1.22 mmol) of aminodiphenylmethane. After 62 h of stirring at rt under N_2, the solvent was evaporated and the residue was chromatographed on silica gel eluting with 40% EtOAc in hexanes to afford 92 mg (44%) of **2f** as a white solid. An analytical sample was obtained by recrystallization from EtOAc−hexanes: mp 138−139 °C; R_f 0.37 (1:1 EtOAc:hexanes); IR ($CHCl_3$) 3420, 1760 (CO) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (d, J = 6.0 Hz, 3H), 2.13 (br s, 1H), 3.43 (qd, J = 6.0, 1.8 Hz, 1H), 3.59 (t, J = 1.8 Hz, 1H), 5.04 (s, 1H), 5.97 (br s, 1H), 7.17−7.35 (m, 6H), 7.38−7.48 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.17, 54.89, 66.38, 72.18, 127.08, 127.32, 127.41, 127.57, 128.54, 128.55, 143.14, 143.27, 169.36; HRMS (FAB) calcd for $C_{17}H_{19}N_2O$ (MH^+) 267.1497, found 267.1490. Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.80; H, 6.56; N, 10.61.

(±)-*trans*-4-Methyl-3-(*N*,*N*-di(2-propenyl)amino)-2-azetidinone (2g), and (±)-2-((*N*,*N*-di(2-propenyl)amino)carbonyl)-*N*,*N*-di(2-propenyl)-1-methylethanamine (13). To a stirred solution of 200 mg (0.783 mmol) of β-lactam **1** in 6.0 mL of anhydrous MeCN at rt under N_2 was added 410 μL (2.35 mmol) of diisopropylethylamine followed by 150 μL (1.22 mmol) of diallylamine. After 67 h of stirring at rt, the solvent was evaporated and the residue was chromatographed on silica gel eluting with 30% EtOAc in hexanes to afford 69 mg (49%) of **2g** as a colorless oil and 29 mg (13%) of **13** as a light brown oil. Compound **2g**: R_f 0.24 (2:3 EtOAc:hexanes); IR (neat) 3270, 1755 (CO) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (d, J = 6.0 Hz, 3H), 3.19−3.36 (m, 4H), 3.75 (qd, J = 6.0, 2.1 Hz, 1H), 3.76 (s, 1H), 5.13−5.26 (m, 4H), 5.76−5.95 (m, 2H), 6.58 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.48, 49.19, 53.93, 76.88, 117.95, 135.08, 169.29; HRMS (FAB) calcd for $C_{10}H_{17}N_2O$ (MH^+) 181.1341, found 181.1319. Compound **13**: R_f 0.63 (2:3 EtOAc:hexanes); IR (neat) 3080, 1640 (CO) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (d, J = 6.3 Hz, 3H), 2.21 (dd, J = 15.6, 6.3 Hz, 1H), 2.30 (br s, 1H), 2.61 (dd, J = 15.6, 6.3 Hz, 1H), 3.14−3.40 (m, 5H), 3.76−4.14 (m, 4H), 5.06−5.26 (m, 8H), 5.67−5.98 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.58, 38.88, 47.68, 49.13, 49.69, 59.13, 116.67, 117.14, 117.98, 132.84, 133.36, 134.67, 171.93; HRMS (FAB) calcd for $C_{16}H_{28}N_3O$ (MH^+) 278.2232, found 278.2252.

(±)-*trans*-3-(*N*-(Methylcarbonyl)-*N*-(phenylmethoxy)-amino)-4-methyl-2-azetidinone (16). To a stirred solution of 215 mg (0.842 mmol) of β-lactam **1** in 10 mL of anhydrous MeCN at rt under N_2 were added 440 μL (2.53 mmol) of diisopropylethylamine and 162 mg (1.32 mmol) of *O*-benzylhydroxylamine. After the solution was stirred at rt under N_2 for 46 h, 240 μL (2.54 mmol) of acetic anhydride was added followed by 210 μL (2.60 mmol) of anhydrous pyridine. After 16 h of stirring at rt, the solvent was evaporated, the residue was dissolved in EtOAc, washed with 1.0 M HCl, saturated $NaHCO_3$, and brine, dried (Na_2SO_4), and filtered, and the solvent was evaporated to afford a colorless oil. The oil was chromatographed using a Chromatotron (2-mm silica gel plate eluting with 40% EtOAc in hexanes) to afford a mixture of **16** and *N*-acetyl-*O*-benzylhydroxylamine as a colorless oil. The oil was dissoved in EtOAc, washed with 5% Na_2CO_3 (with a small amount of a 1.0 M NaOH solution added) and brine, dried (Na_2SO_4), and filtered, and the solvent was evaporated to afford a colorless oil. The oil was chromatographed using a Chromatotron (1-mm silica gel plate eluting with 50% EtOAc in hexanes) to afford 20 mg (10%) of **16** as a colorless oil: R_f 0.21 (1:1 EtOAc:hexanes); IR ($CHCl_3$) 3430, 1770 (CO), 1675 (CO) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (d, J = 6.2 Hz, 3H), 2.19 (s, 3H), 3.94 (qd, J = 6.2 Hz, 2.4 Hz, 1H), 4.93 (d, J = 9.8 Hz, 1H), 5.11 (d, J = 1.6 Hz, 1H), 5.16 (d, J = 9.8 Hz, 1H), 6.15 (br s, 1H), 7.39 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.33, 20.47, 50.67, 70.35, 78.63, 128.69, 129.04, 129.46, 134.21, 165.29, 173.59; HRMS (FAB) calcd for $C_{13}H_{17}N_2O_3$ (MH^+) 249.1239, found 249.1264.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **2d**, **2g**, **3a/b**, **4b**, **13**, and **16** (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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