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SYNTHESIS OF α-AMINO KETONES AND *O*-ALKYLOXIMES BY TITANIUM TETRAHALIDE PROMOTED RING-OPENING REACTION OF 2-MONO-SUBSTITUTED AZETIDIN-3-ONES AND THEIR *O*-ALKYLOXIMES

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Abstract – Synthesis of α-amino ketones and *O*-alkyloximes has been developed by titanium tetrahalide-promoted ring-opening reactions of 2-mono-substituted azetidin-3-ones and their *O*-alkyloximes. Regarding the reductive ring-opening reactions of 2-mono-substituted azetidin-3-ones, an appropriate use of TiI_4 or TiI_4-$TiCl_4$ as a promoter gave α-amino ketones in good yields with high regioselectivities. In $TiBr_4$-promoted ring-opening reactions, while use of 2-mono-substituted azetidin-3-ones as a substrate provided α-amino-α'-bromo ketones generated by the attack of the bromide anion at the less hindered site, those of 2-mono-substituted azetidin-3-one *O*-alkyloximes proceeded at the more hindered site to give α-amino-α'-bromo ketone *O*-alkyloximes in good yields.

INTRODUCTION

α-Amino ketones are one of the most important nitrogen-containing compounds because of their use as versatile building blocks and intermediates for the biologically active compound synthesis.[1] Several methods for the synthesis of α-amino ketones have been reported.[2] We have reported titanium tetraiodide (TiI_4)-promoted reductive aldol, Michael, and Mannich-type reactions by the reductive generation of enolates via ring-opening of small-sized heterocyclic compounds such as alkoxyallene oxides **1** or aziridine derivatives **2a-c** bearing electron-withdrawing groups (Scheme 1).[3] Azetidin-3-ones **3** have not been well studied compared with their 2-one analogues (β-lactams) because azetidin-3-ones **3** do not exist in nature. However, azetidin-3-ones **3** have been used as intermediates for the synthesis of natural

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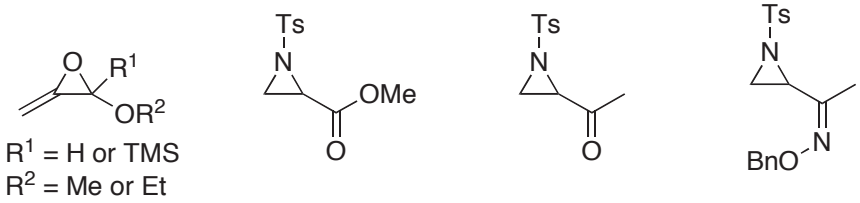
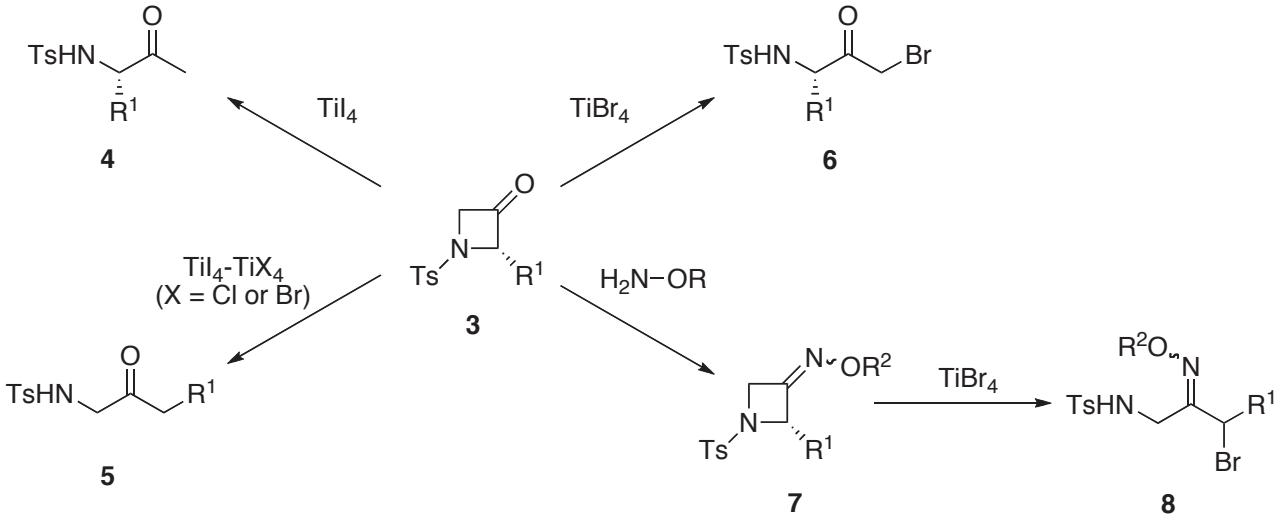
This paper is dedicated to Professor Ei-ichi Negishi on the occasion of his 77th birthday.

products and biologically active compounds containing an azetidine ring because of ready availability from α-amino acids.[4,5] We focused on the ring-opening reaction of azetidin-3-ones **3** by titanium tetrahalide for the synthesis of α-amino ketones. Herein we describe synthesis of α-amino ketones **4**-**6** and *O*-alkyloximes **8** from 2-mono-substitued azetidin-3-ones **3** by the use of titanium tetrahalide (Scheme 2).[6]



Scheme 1. Alkoxyallene Oxides **1** and Aziridine Derivatives **2a**-**c**

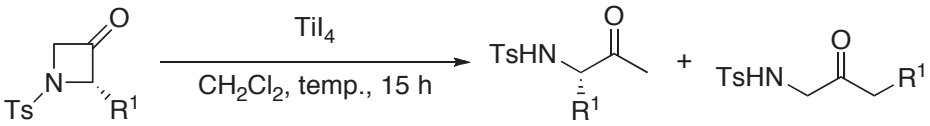


Scheme 2. Synthesis of α-Amino Ketones and *O*-Alkyloximes

RESULTS AND DISCUSSION

We examined the ring-opening reaction of several azetidin-3-ones **3** with TiI_4.[6a] Table 1 summarizes the results. The ring-opening reaction of azetidin-3-one **3a** using TiI_4 proceeded smoothly to give α-amino ketone **4a** in 80% yield (entry 1). The ring-opening reactions of several 2-mono-substituted azetidin-3-ones were next examined. The reaction of 2-methyl-azetidin-3-one **3b** gave a mixture of α-amino ketones **4b** and **5b** in high yield with high regioselectivity (entry 2). When azetidin-3-ones **3c** (R^1 = Et) and **3d** (R^1 = ^{i}Pr) were used, both yields and regioselectivities slightly decreased (entries 3 and 4). Although the reaction of 2-isobutyl-3-azetidin-3-one **3e** gave α-amino ketones **4e** and **5e** in high yield, the regioselectivity was moderate (entry 5). The reaction of 2-benzyl-3-azetidin-3-one **3f** gave a mixture of α-amino ketones **4f** and **5f** in good yield with high regioselectivity (entry 6).

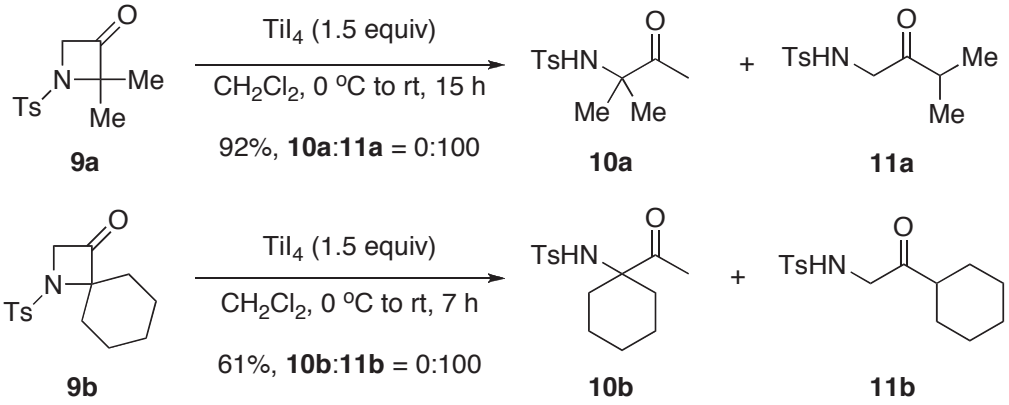
Table 1. TiI_4-promoted Ring-opening Reaction of Azetidin-3-ones **3**



Entry	R^1	**3**	TiI_4 (equiv)	Temp	Yield[a]	**4**:**5**[b]
1	H	**3a**	3.0	0 °C to rt	80	—
2	Me	**3b**	2.0	0 °C to rt	89	95:5
3	Et	**3c**	1.5	rt	66	83:17
4	^{i}Pr	**3d**	3.0	rt	76	77:23
5	^{i}Bu	**3e**	2.0	0 °C to rt	97	63:37
6	Bn	**3f**	3.0	rt	82	92:8

[a]Each regioisomer was not separated. [b]Ratios were determined by ^{1}H NMR spectra.

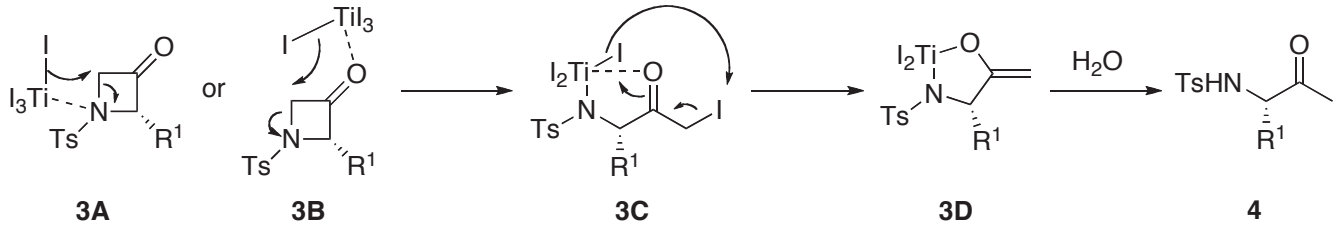
In the reductive ring-opening reaction of 2-mono-substituted azetidin-3-ones by TiI_4, C-N bond cleavages occurred at the less sterically congested bond to give the α-amino ketone **4** preferentially. On the other hand, C-N bond cleavages of 2,2-disubstituted azetidin-3-ones **9** proceeded at the more substituted bond to afford the ketones **11** as sole products (Scheme 3).



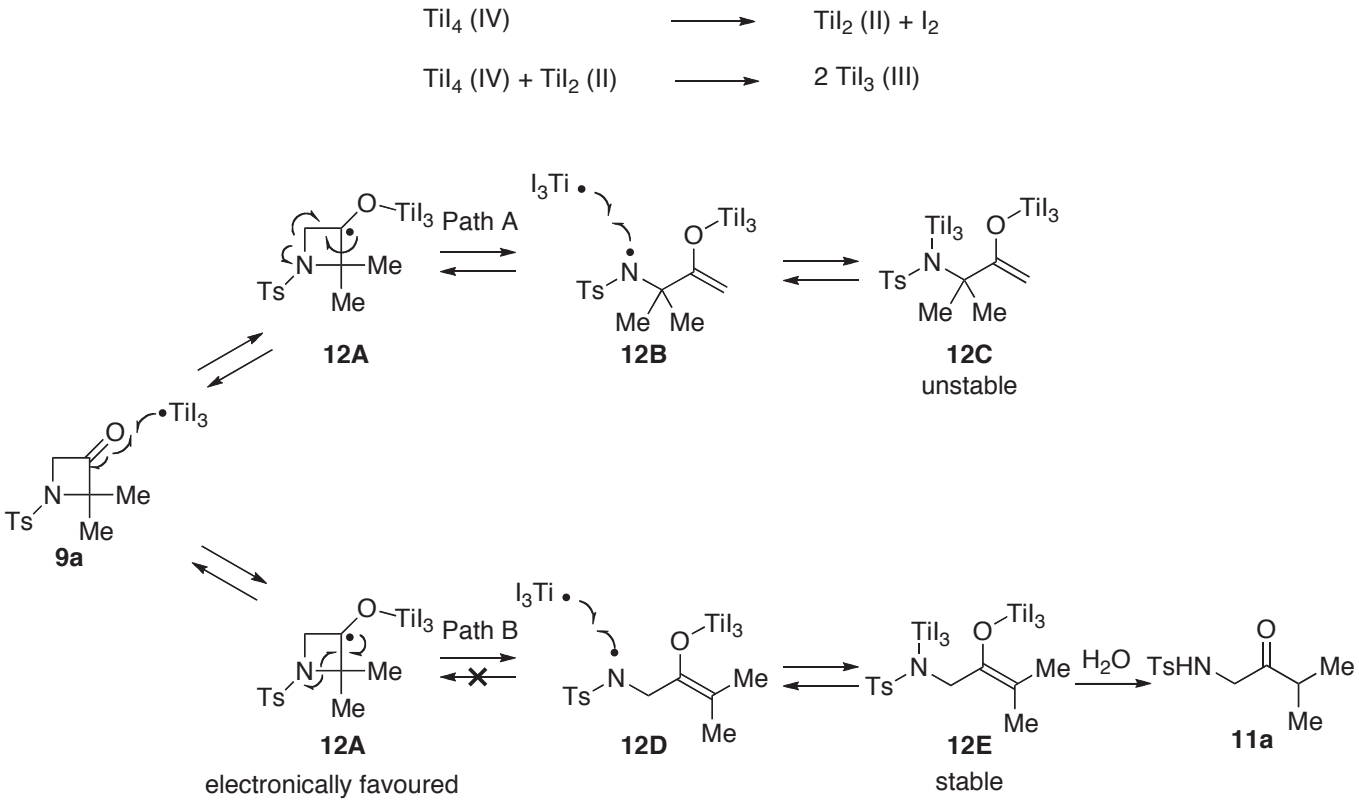
Scheme 3. Ring-opening Reaction of 2,2-Disubstituted Azetidin-3-ones **9**

Regarding the different regioselectivity, we proposed two different pathways including an S_N2-like process by TiI_4 or a one-electron transfer promoted by low-valent titanium species. In the case of 2-mono-substituted azetidin-3-ones **3**, the reaction would prefer an S_N2-like process rather than one electron transfer, because radical stabilization is more depressed as compared with that of 2,2-disubstited cases. Initially, α-iodoketone **3C** is generated via the ring-opening of azetidin-3-ones **3A** or **3B** attacked by the iodide anion at the less hindered site and subsequently another iodide anion attacks to the iodine to

generate the titanium enolate species **3D**. Hydrolysis of the enolate **3D** with water to quench the reaction gives the α-amino ketone **4** (Scheme 4).



Scheme 4. Plausible Reaction Mechanism in the Ring-opening of 2-Mono-substituted Azetidin-3-ones **3**



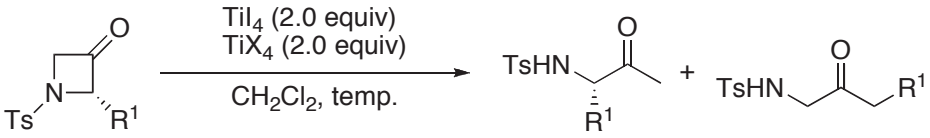
Scheme 5. Plausible Reaction Mechanism in the Ring-opening of 2,2-Dimethyl-azetidin-3-ones **9a**

In the case of 2,2-dimethyl-azetidin-3-ones **9a**, it seems that an electron-transfer reaction would play a significant role (Scheme 5). Initially, the disproportion of TiI_4 gives low-valent titanium species. One-electron transfer to azetidin-3-one at the C-3 position gives a radical intermediate **12A**. A ring-opening reaction proceeded via a fragmentation at the N-C(2) or N-C(4) bond. At this point, the fragmentation at the N-C(2) bond was favored because of the electronically more stabilized 2,2-dimethyl substitution. Further reduction of the intermediate leads to the corresponding titanium enolate. Also, the homolysis of the N-C(4) bond gives the less substituted enolate **12C** (path A). Alternatively, the homolysis of the

N-C(2) bond leads to the more substituted enolate **12E** (path B). In path A, the enolate **12C** could reverse to the azetidine **9a** via a re-cyclization under equilibrium.[7] However, path B may not involve such a cyclization because of the steric hindrance. Finally, the more thermodynamically stable enolate **12E** would predominate. The enolate **12E** is hydrolyzed with water to give the α-amino ketone **11a**.

In order to facilitate the ring-opening reaction of 2-mono-substituted azetidin-3-ones at the more substituted bond, several additives were next examined. When a combined use of TiI_4 and titanium chloride ($TiCl_4$) or bromide ($TiBr_4$) was undertaken, ring-opening of several 2-mono-substituted azetidin-3-ones **3b**-**e** occurred at the more substituted bond to give the α-amino ketones **5b**-**e** preferentially.[6b] Table 2 summarizes the results. Although TiI_4-$TiBr_4$ promoted ring-opening reaction proceeded to give α-amino ketones with good to high regioselectivities, the yields were not satisfied in some cases (entries 1-4). On the other hand, when the ring-opening reactions were carried out with TiI_4-$TiCl_4$ as a promoter, α-amino ketones were obtained in moderate to high yields with higher regioselectivities.

Table 2 TiI_4-TiX_4 (X = Br or Cl) Promoted Ring-opening Reaction of 2-Mono-substituted Azetidin-3-ones



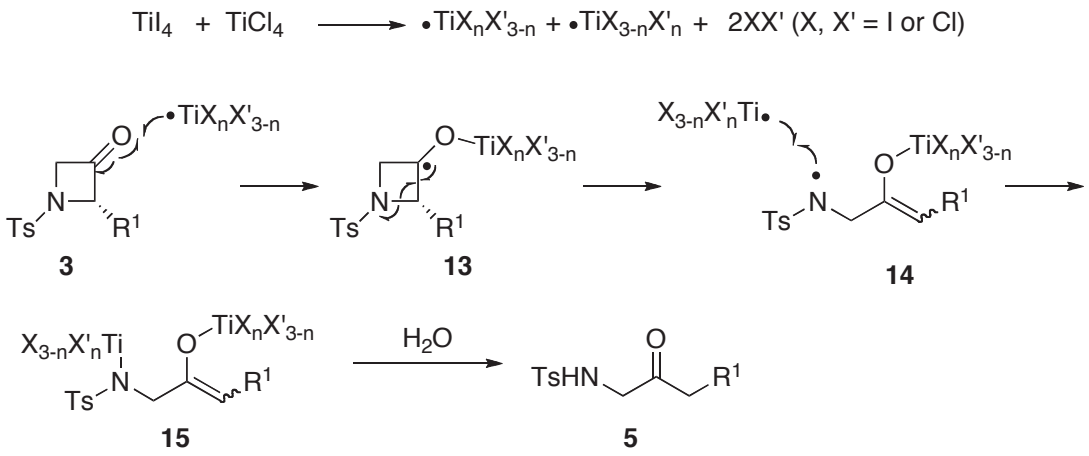
3b-e **4b-e** **5b-e**

Entry	R^1	**3**	X	Temp.	Time (h)	Yield (%)[a]	**4**:**5**[b]
1	Me	**3b**	Br	–78 ºC to rt	17	26	25:75
2	Et	**3c**	Br	–78 ºC to rt	17	30	4:96
3	^{i}Pr	**3d**	Br	–78 ºC to rt	17	56	0:100
4	^{i}Bu	**3e**	Br	–20 to 10 ºC	15	90	16:84
5	Me	**3b**	Cl	0 ºC to rt	17	63	9:91
6	Et	**3c**	Cl	0 ºC to rt	17	78	4:96
7	^{i}Pr	**3d**	Cl	–78 ºC to rt	21	84	0:100
8	^{i}Bu	**3e**	Cl	–78 ºC to rt	15	88	0:100

[a]Each regioisomer was not separated. [b]Ratios were determined by ^{1}H NMR spectra.

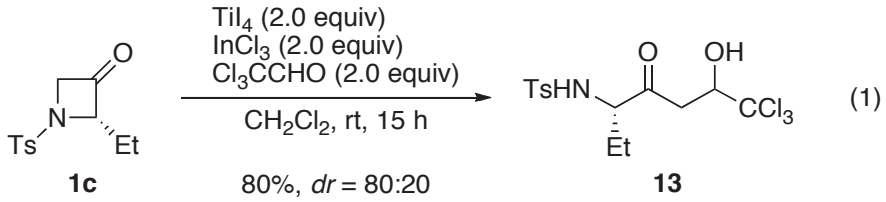
A plausible reaction mechanism is shown in Scheme 6. The disproportion of TiI_4 and $TiCl_4$ gives low-valent titanium species. A one-electron transfer to 2-mono-substituted azetidin-3-one **3** at the C-3 position gives a radical intermediate **13**. The ring-opening reaction of **13** would proceed via a fragmentation at the N-C(2) bond to give the more substituted titanium enolate **15**, which is more stable

than the less substituted one, and the subsequent protonation with water to quench the reaction would give the corresponding α-amino ketone **5**.

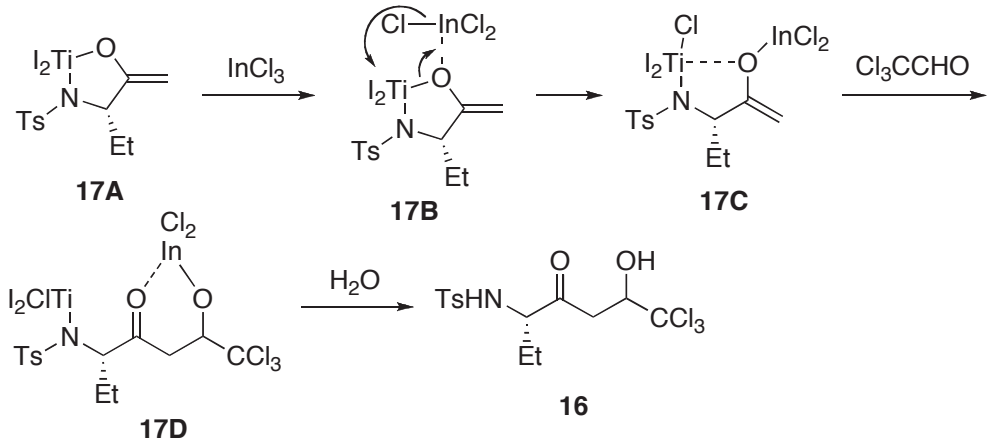


Scheme 6. Plausible Reaction Mechanism in TiI_4-$TiCl_4$ Promoted Ring-opening Reaction

The reductive aldol reaction of the enolate generated in situ was next examined. TiI_4-promoted reductive aldol reaction of 2-ethyl-azetidin-3-one **3c** with chloral proceeded smoothly in the presence of $InCl_3$ as a Lewis acid additive to give the adduct **16** in 80% yield with moderate diastereoselectivity (Eq. 1).

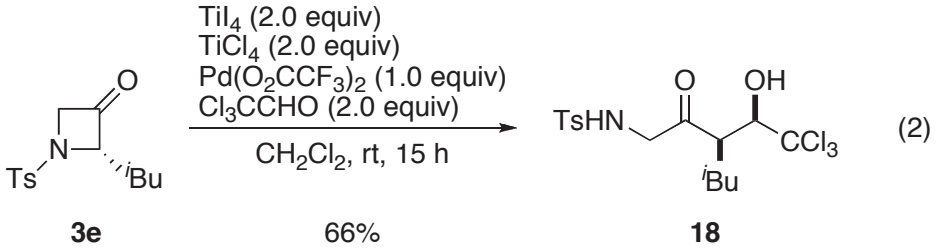


The role of $InCl_3$ may be explained in terms of the formation of a more reactive enolate **17C** from the stable titania cycle **17A**. Finally, the indium enolate **17C** reacts with chloral to give the aldol adduct **16**.



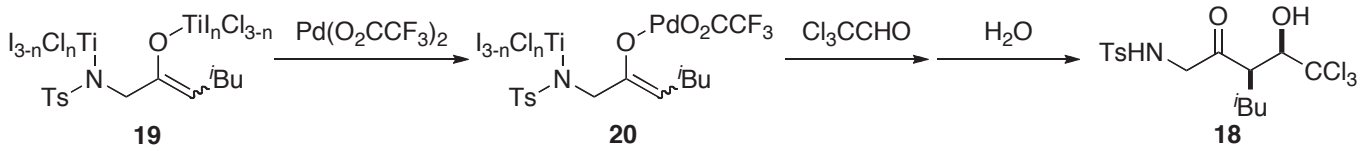
Scheme 7. Plausible Reaction Mechanism for Aldol Reaction via a Ring-opening Reaction at the Less Substituted Carbon

When the reaction of 2-isobutyl-azetidin-3-one **3e** with chloral was carried out using TiI_4-$TiCl_4$ in the presence of $Pd(O_2CCF_3)_2$ as a Lewis acid additive, the aldol adduct **18** was obtained in 66% yield with *syn*-selectivity (eq. 2).



(2)

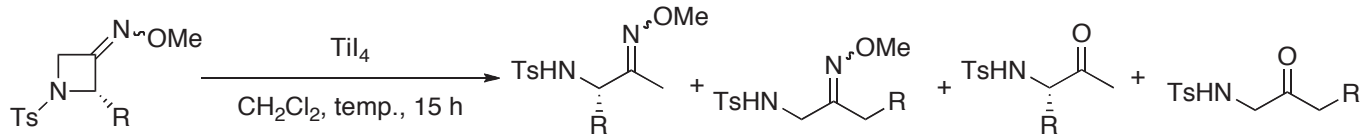
Although the role of $Pd(O_2CCF_3)_2$ is not yet clear, we presumed that a transmetallation of titanium to palladium would occur to generate the palladium enolate **20**, which would react with chloral to give the aldol adduct **18**.



Scheme 8. Plausible Reaction Mechanism for Aldol Reaction via a Ring-opening Reaction at the More Substituted Carbon

When aldehydes other than reactive chloral were used under the each aldol reaction conditions, the desired aldol adducts were obtained in low yield because of less reactivity of the metal enolates generated in situ. We next examined the ring-opening reaction of 2-mono-substituted azetidine-3-one *O*-alkyloximes to generate aza-enolates, which enhance the nucleophilicity as compared with their parent carbonyl compounds.[8] Table 3 summarizes the results. TiI_4-promoted ring-opening reaction of 2-mono-substituted azetidin-3-one *O*-alkyloxime proceeded at the more hindered site. The ring-opening reaction of **7a** gave α-amino ketone **5b** in 51% yield accompanied by α-amino ketone **4b** in 2% yield (entry 1). Although the ring-opening reactions of both azetidin-3-one *O*-alkyloximes **7b** and **7c** also proceeded at the more hindered site to give the α-amino ketones, the yields decreased (entries 2 and 3). In every reaction, a mixture of α-amino ketones **4** and **5** was obtained instead of the desired α-amino ketone *O*-alkyloximes probably due to the reductive cleavage of the N-O bond by TiI_4 and subsequnt hydrolysis with water to quench the reaction.

Table 3. TiI_4-promoted Ring-opening Reaction of Azetidin-3-one *O*-Alkyloximes

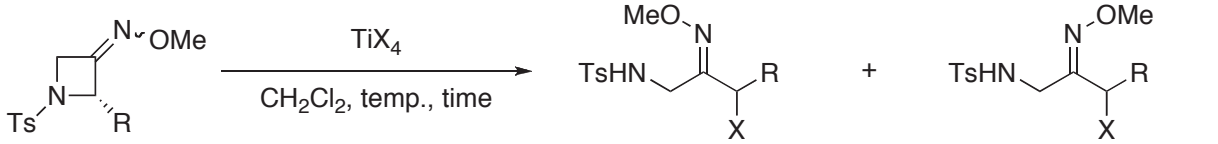


						Yield (%)			
Entry	R	**7**	TiI_4 (equiv)	Temp.	Time (h)	**21**	**22**	**4**	**5**
1	Me[a]	**7a**	2.0	rt	19	0	0	2	51
2	Et[b]	**7b**	3.0	rt	24	0	0	1	35
3	^{i}Bu[c]	**7c**	2.0	0 °C to rt	15	0	0	0	28

[a]*E*:*Z* = 31:69. [b]*E*:*Z* = 33:67. [c]*E*:*Z* = 30:70.

It was of interest that the regioselectivity of the ring-opening reaction of 2-mono-substituted azetidin-3-one *O*-alkyloximes was different from that of the parent 2-mono-substituted azetidin-3-ones. We next examined the ring-opening reaction of 2-mono-substituted azetidine-3-one *O*-alkyloximes by $TiCl_4$ and $TiBr_4$ to obtain the desired α-amino ketone *O*-alkyloximes because their reducing abilities are less than that of TiI_4. $TiCl_4$-promoted ring-opening reaction of 2-methyl-azetidin-3-one *O*-methyloxime **7a** proceeded under the several reaction conditions to give a mixture of α-amino ketone *O*-methyloximes **(*E*)-** and **(*Z*)-8a-Cl** in high yields with high regioselectivities (entries 1-4). The reaction of **7a** with $TiBr_4$ at room temperature for 20 h gave a mixture of α-amino ketone *O*-methyloximes **(*E*)-** and **(*Z*)-8a-Br** in 59% yield with the same high regioselectivities as in the case with $TiCl_4$ (entry 5). When the reaction of **7a** was carried out at 0 °C to room temperature for 4 h, the yield increased to 93% (entry 6). Use of 1.5 equivalents of $TiBr_4$ gave the best 97% yield (entry 7). $TiBr_4$-promoted ring-opening reactions of 2-isopropylazetidin-3-one *O*-methyloxime **7d** with several *E* and *Z* ratios were carried out to give a mixture of α-amino ketone *O*-methyloximes **(*E*)-** and **(*Z*)-8d-Br** in good yields. (entries 9-11).

Table 4. $TiCl_4$ or $TiBr_4$-promoted Ring-opening Reaction of Azetidin-3-one *O*-Alkyloximes



7a: R = Me
7d: R = ^{i}Pr

(*E*)-8a-Cl: R^1 = Me, R^2 = Cl
(*E*)-8a-Br: R^1 = Me, R^2 = Br
(*E*)-8d-Br: R^1 = ^{i}Pr, R^2 = Br

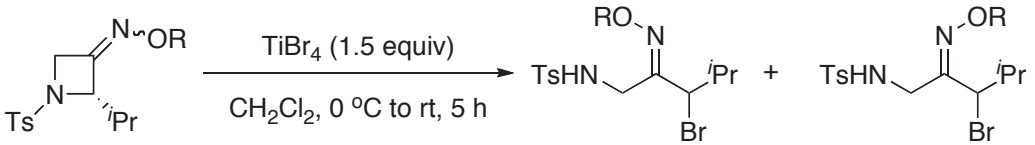
(*Z*)-8a-Cl: R^1 = Me, R^2 = Cl
(*Z*)-8a-Br: R^1 = Me, R^2 = Br
(*Z*)-8d-Br: R^1 = ^{i}Pr, R^2 = Br

Entry	R	**7**	X (equiv)	Temp.	Time (h)	Yield (%)	***E*:*Z***
1	Me[a]	**7a**	Cl (2.0)	rt	20	88	68:32
2	Me[a]	**7a**	Cl (2.0)	0 ºC to rt	4	88	66:34
3	Me[a]	**7a**	Cl (1.5)	0 ºC to rt	5	87	69:31
4	Me[a]	**7a**	Cl (1.0)	0 ºC to rt	7	86	71:29
5	Me[a]	**7a**	Br (2.0)	rt	20	59	58:42
6	Me[a]	**7a**	Br (2.0)	0 ºC to rt	4	93	62:38
7	Me[a]	**7a**	Br (1.5)	0 ºC to rt	5	97	67:33
8	Me[a]	**7a**	Br (1.0)	0 ºC to rt	7	58	74:26
9	^{i}Pr[b]	**7d**	Br (1.5)	0 ºC to rt	5	77	46:54
10	^{i}Pr[c]	**7d**	Br (1.5)	0 ºC to rt	5	78	53:47
11	^{i}Pr[d]	**7d**	Br (1.5)	0 ºC to rt	5	75	68:32

[a]*E*:*Z* = 31:69. [b]*E*:*Z* = 0:100. [c]*E*:*Z* = 18:82. [d]*E*:*Z* = 100:0.

In order to improve the *E*-*Z* ratios, we next examined the reaction of the sterically hindered α-amino ketone *O*-alkyloxime. Table 5 summarizes the results. $TiBr_4$-promoted ring-opening reaction of 2-isopropyl-azetidin-3-one *O*-*tert*-butyloxime **7e** proceeded to give only the α-amino ketone *O*-*tert*-butyloxime **(*E*)-8e-Br** in moderate yields regardless of the geometry of **7e**. The reaction of 2-isopropylazetidin-3-one *O*-isopropyloxime **7f** also gave the α-amino ketone *O*-isopropyl oxime **8f-Br** in good yield with *E* selectivity regardless of the geometry of **7f**. The yields using **7e** were lower than those using **7f** because a *tert*-butyl group is more sensitive to Lewis acidic conditions than an isopropyl group.

Table 5. $TiBr_4$-promoted Ring-opening Reaction of Azetidin-3-one *O*-Alkyloximes

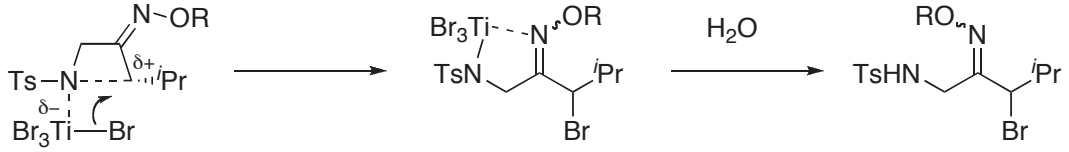


7e: R = ^{t}Bu
7f: R = ^{i}Pr

(***E*)-8e-Br**: R = ^{t}Bu
(***E*)-8f-Br**: R = ^{i}Pr

(***Z*)-8e-Br**: R = ^{t}Bu
(***Z*)-8f-Br**: R = ^{i}Pr

Entry	R	**7**	Yield (%)	***E*:*Z***
1	^{t}Bu	(*E*)-**7e**	42	100:0
2	^{t}Bu	(*Z*)-**7e**	33	100:0
3	^{i}Pr	(*E*)-**7f**	78	95:5
4	^{i}Pr	(*Z*)-**7f**	77	97:3



23 **24** **8**

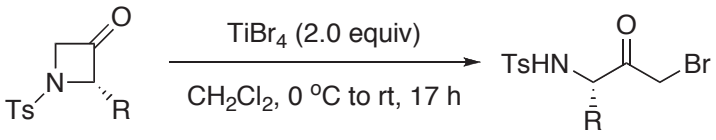
Scheme 9. Plausible Reaction Mechanism for the Ring-opening Reaction of Azetidin-3-one *O*-Alkyloximes Promoted by $TiBr_4$

From the results in both Tables 4 and 5, $TiBr_4$ activates the tosylamide nitrogen because geometry of the oxime ether did not affect the regioselectivity. An S_N2-like reaction occurs at the carbon having a partially positive charge to generate the intermediate **24** (Scheme 9).

The ring-opening reactions of several azetidine-3-ones by $TiBr_4$ were carried out. Table 6 summarizes the results. The ring-opening reactions of several azetidin-3-ones **3** proceeded to give α-amino-α'-bromo ketones **6** in moderate to good yields with high regioselectivities.

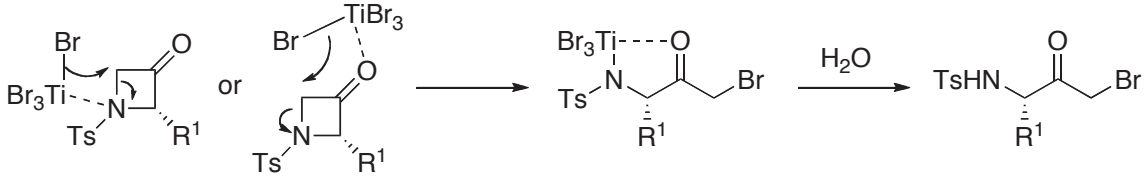
Regarding the different regioselectivity between azetidin-3-ones and azetidin-3-one *O*-alkyloximes in $TiBr_4$-promoted ring-opening reactions, we presume that one of the reasons is the difference of the electron-withdrawing ability between carbonyl and imino groups. A carbonyl group, which is more electron-withdrawing than an imino group, destabilizes the partially positive charge, and therefore, the ring-opening reactions of azetidin-3-ones **3E** or **3F** proceed by the attack of the bromide anion at the less hindered site to give the α-amino-α'-bromo ketones **6** via the intermediate **3G** (Scheme 10).

Table 6. $TiBr_4$-promoted Ring-opening Reaction of Azetidin-3-ones



3b-f **6b-f**

Entry	R	**3**	Yield (%)	Entry	R	**3**	Yield (%)
1	Me	**3b**	59	3	^{i}Pr	**3d**	69
2	Et	**3c**	72	4	^{i}Bu	**3e**	89



3E **3F** **3G** **6**

Scheme 10. Plausible Reaction Mechanism for the Ring-opening Reaction of Azetidin-3-one Promoted by $TiBr_4$

CONCLUSIONS

Synthesis of α-amino ketones and *O*-alkyloximes has been developed by titanium tetrahalide-promoted ring-opening reactions of 2-mono-substituted azetidin-3-ones and their *O*-alkyloximes. In the reductive ring-opening reactions of 2-mono-substituted azetidin-3-ones, an appropriate use of TiI_4 or TiI_4-$TiCl_4$ as a promoter gave α-amino ketones **4** or **5** in good yields with high regioselectivities. Reductive aldol reactions of enolates with chloral proceeded in the presence of Lewis acid additives such as $InCl_3$ and $Pd(O_2CCF_3)_2$ to give the aldol adducts in good yields. In $TiBr_4$-promoted ring-opening reactions, while use of 2-mono-substituted azetidin-3-ones as a substrate gave α-amino-α'-bromo ketones **6** generated by the attack of the bromide anion at the less hindered site, the reaction of 2-mono-substituted azetidin-3-one *O*-alkyloximes **7** proceeded at the more hindered site to give α-amino-α'-bromo ketone *O*-alkyloximes **8** in good yields.

EXPERIMENTAL

General. Infrared spectra were recorded on a JASCO FT/IR-460 Plus spectrometer. ^{1}H NMR spectra were recorded on a JEOL ECX- 400 spectrometer (400 MHz) or a JEOL JNM α- 500 spectrometer (500 MHz) with tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded on a JEOL ECX-400 spectrometer (100.5 MHz) or a JEOL JNM α- 500 spectrometer (126 MHz). Chemical sifts are reported in δ units, parts per million from the central peak of $CDCl_3$ (δ 77.0) as an internal reference. High resolution mass spectra (EI) were recorded on a JEOL JMS-700D mass spectrometer. Dichloromethane (CH_2Cl_2) was pre-dried with P_2O_5, distilled from CaH_2, and stored over molecular sieves 4A. Purification of products was performed by column chromatography on silica gel (Kanto Chemical Co. Inc., Silica Gel 60 N (spherical, neutral)) and/or preparative TLC on silica gel (Merck Kiesel Gel GF254). All reactions were carried out under an argon atmosphere. Various azetidin-3-ones were synthesized according to the previously reported literatures.[9-13]

Typical procedure (Table 1, entry 1): A solution of *N*-*p*-tosyl-azetidin-3-one (**3a**) (22.5 mg, 0.10 mmol) in CH_2Cl_2 (1.0 mL) was added to a solution of titanium tetraiodide (166.6 mg, 0.30 mmol) in CH_2Cl_2 (2.0 mL) at 0 ºC. The reaction mixture was allowed to warm to ambient temperature with stirring for 15 h. The reaction was quenched with sat. aq. $NaHCO_3$. The whole mixture was diluted with EtOAc (5.0 mL), followed by the addition of 10% aq. $NaHSO_3$. The mixture was filtered through a Celite pad. The layers were separated, and the aqueous layer was extracted with ethyl acetate (20 mL x 3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by preparative TLC on silica gel (*n*-hexane/CH_2Cl_2/Et_2O = 2/3/2) to give 1-(tosylamino)propan-2-one (**4a**) (18.2 mg, 80%).

1-(Tosylamino)propan-2-one (4a):

White solid. Mp 96-97 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 2.11 (s, 3H), 2.42 (s, 3H), 3.85 (d, *J* = 4.6 Hz, 2H), 5.31 (t, *J* = 4.6 Hz, 1H), 7.29-7.32 (m, 2H), 7.72-7.75 (m, 2H). ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ = 21.5, 27.1, 52.1, 127.1, 129.8, 136.1, 143.8, 201.0. IR (neat) 3279, 3038, 2970, 1718, 1407, 1363, 1343, 1162, 1103, 1094, 816, 706, 546 cm^{-1}. HRMS (EI): Calculated for $C_{13}H_{19}NO_3S$ $(M)^+$ 227.0616, found 227.0613.

3-(Tosylamino)butan-2-one (4b):

White solid. Mp 71-72 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.35 (d, *J* = 7.3 Hz, 3H), 2.09 (s, 3H), 2.42 (s, 3H), 3.93 (dq, *J* = 6.2, 7.3 Hz, 1H), 5.52 (d, *J* = 6.2 Hz, 1H), 7.28-7.31 (m, 2H), 7.70-7.73 (m, 2H). ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ = 18.8, 21.5, 26.2, 57.6, 127.1, 129.7, 136.9, 143.7, 205.5. IR (neat) 3276, 2984, 2928, 1717, 1598, 1424, 1335, 1163, 1127, 1092, 816, 667, 551 cm^{-1}. HRMS (EI): Calculated for $C_9H_{12}NO_2S$ $(M\text{-}C_2H_3O)^+$ 198.0589, found 198.0592.

1-(Tosylamino)butan-2-one (5b):

White solid. Mp 83-84 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.03 (t, *J* = 7.3 Hz, 3H), 2.37 (q, *J* = 7.3 Hz, 2H), 2.42 (s, 3H), 3.83 (d, *J* = 4.6 Hz, 2H), 5.29 (t, *J* = 4.6 Hz, 1H), 7.29-7.32 (m, 2H), 7.72-7.75 (m, 2H). ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ = 7.5, 21.5, 33.4, 51.0, 127.2, 129.8, 136.1, 143.8, 204.0. IR (neat) 3280, 2973, 2922, 1717, 1411, 1328, 1163, 1094, 814, 547 cm^{-1}. HRMS (EI): Calculated for $C_8H_{10}NO_2S$ $(M\text{-}C_3H_5O)^+$ 184.0432, found 184.0437.

3-(Tosylamino)pentan-2-one (4c):

White solid. Mp 74-75 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.86 (dd, *J* = 7.3, 7.3 Hz, 3H), 1.62 (ddq, *J* = 6.9, 7.3, 14.4 Hz, 1H), 1.87 (ddq, *J* = 4.8, 7.3, 14.4 Hz, 1H), 2.04 (s, 3H), 2.41 (s, 3H), 3.89 (ddd, *J* = 4.8, 6.6, 6.9 Hz, 1H), 5.47 (d, *J* = 6.6 Hz, 1H), 7.26-7.30 (m, 2H), 7.69-7.72 (m, 2H). ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ = 8.7, 21.5, 25.3, 26.6, 62.8, 127.1, 129.7, 136.8, 143.6, 205.3. IR (neat) 3273, 2972, 2935, 2925, 1715, 1598, 1453, 1422, 1334, 1251, 1163, 1125, 1092, 816, 670 cm^{-1}. HRMS (EI): Calculated for $C_{10}H_{14}NO_2S$ $(M\text{-}C_2H_3O)^+$ 212.0745, found 212.0752.

1-(Tosylamino)pentan-2-one (5c):

White solid. Mp 81-82 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.84 (t, *J* = 7.3 Hz, 3H), 1.55 (tq, *J* = 7.3, 7.3 Hz, 2H), 2.31 (t, *J* = 7.3 Hz, 2H), 2.42 (s, 3H), 3.82 (d, *J* = 4.8 Hz, 2H), 5.30 (t, *J* = 4.8 Hz, 1H), 7.29-7.32 (m, 2H), 7.72-7.54 (m, 2H). ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ = 13.5, 17.1, 21.5, 41.9, 51.4, 127.2, 129.8, 136.1, 143.8, 203.6. IR (neat) 3277, 2956, 2918, 1717, 1597, 1445, 1407, 1321, 1159, 1163, 1088, 810, 668 cm^{-1}. HRMS (EI): Calculated for $C_8H_{10}NO_2S$ $(M\text{-}C_4H_7O)^+$ 184.0432, found 184.0435.

4-Methyl-3-(tosylamino)pentan-2-one (4d):

White solid. Mp 77-78 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.72 (d, *J* = 6.9 Hz, 3H), 1.05 (d, *J* = 6.9 Hz, 3H), 1.97 (s, 3H), 2.07 (dsept, *J* = 3.7, 6.9 Hz, 1H), 2.41 (s, 3H), 3.81 (dd, *J* = 3.7, 8.7 Hz, 1H), 5.35 (d, *J* = 8.7 Hz, 1H), 7.26-7.29 (m, 2H), 7.67-7.70 (m, 2H). ^{3}C-NMR (100.5 MHz, $CDCl_3$) δ = 16.1, 19.9, 21.5, 27.5, 30.1, 66.9, 127.2, 129.6, 136.7, 143.6, 205.7. IR (neat) 3276, 3055, 2967, 2925, 2870, 1719, 1599, 1451, 1408, 1330, 1251, 1161, 1128, 1093, 1039, 856, 812, 670, 546 cm^{-1}. HRMS (EI): Calculated for $C_{11}H_{16}NO_2S$ $(M\text{-}C_2H_3O)^+$ 226.0902, found 226.0893.

4-Methyl-1-(tosylamino)pentan-2-one (5d):

White solid. Mp 63-65 ºC. ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 0.82 (d, *J* = 6.7 Hz, 6H), 2.03 (tsept, *J* = 6.7, 7.0 Hz, 1H), 2.20 (d, *J* = 7.0 Hz, 2H), 2.42 (s, 3H), 3.80 (d, *J* = 4.6 Hz, 2H), 5.35 (t, *J* = 4.6 Hz, 1H), 7.29-7.31 (m, 2H), 7.72-7.74 (m, 2H). ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ = 21.5, 22.3, 24.7, 48.9, 51.8, 127.2, 129.8, 136.0, 143.8, 203.3. IR (neat) 3275, 2956, 2925, 2869, 1716, 1600, 1322, 1161, 1038, 814, 688 cm^{-1}. HRMS (EI): Calculated for $C_8H_{10}NO_2S$ $(M\text{-}C_5H_9O)^+$ 184.0432, found184.0434.

5-Methyl-3-(tosylamino)hexan-2-one (4e):

White solid. Mp 59-60 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.87 (d, *J* = 2.7 Hz, 3H), 0.88 (d, *J* = 2.7 Hz, 3H), 1.31 (ddd, *J* = 4.5, 9.7, 14.0 Hz, 1H), 1.42 (ddd, *J* = 4.0, 9.7, 14.0 Hz, 1H), 1.83 (m, 1H), 2.00 (s, 3H), 2.41 (s, 3H), 3.90 (ddd, *J* = 4.0, 8.4, 9.7 Hz, 1H), 5.31 (d, *J* = 8.4 Hz, 1H), 7.27-7.30 (m, 2H), 7.68-7.71 (m, 2H). ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ = 21.4, 23.3, 24.5, 26.8, 41.2, 60.7, 127.3, 129.8, 136.8, 143.8, 206.5. IR (neat) 3238, 2957, 2875, 1722, 1597, 1161, 1088, 1039, 821, 664 cm^{-1}. HRMS (EI): Calculated for $C_{12}H_{18}NO_2S$ $(M\text{-}C_2H_3O)^+$ 240.1058, found 240.1061.

5-Methyl-1-(tosylamino)hexan-2-one (5e):

White solid. Mp 82-83 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.83 (d, *J* = 6.2 Hz, 6H), 1.42 (m, 3H), 2.32 (t, *J* = 7.6 Hz, 2H), 2.42 (s, 3H), 3.83 (d, *J* = 4.5 Hz, 2H), 5.34 (t, *J* = 4.5 Hz, 1H), 7.29-7.32 (m, 2H), 7.72-7.75 (m, 2H). ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ = 22.2, 22.3, 27.6, 32.4, 38.2, 51.3, 127.3, 129.6, 136.1, 143.9, 204.1. IR (neat) 3284, 3067, 2954, 2872, 1719, 1602, 1160, 1064, 813, 679 cm^{-1}. HRMS (EI): Calculated for $C_{13}H_{19}NO_3S$ $(M)^+$ 283.1242, found 283.1246.

4-phenyl-3-(tosylamino)butan-2-one (4f):

White semisolid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 2.02 (s, 3H), 2.40 (s, 3H), 2.91 (dd, *J* = 6.4, 14.0 Hz, 1H), 2.98 (dd, *J* = 6.4, 14.0 Hz, 1H), 4.10 (dt, *J* = 6.4, 7.3 Hz, 1H), 5.22 (d, *J* = 7.3 Hz, 1H), 7.01-7.04 (m, 2H), 7.20-7.26 (m, 5H), 7.56-7.59 (m, 2H). ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ = 14.5, 20.6, 31.3, 55.6, 120.1, 120.3, 121.8, 122.2, 122.7, 127.9, 129.6, 136.7, 198.8. IR (neat) 3279, 2922, 2852, 1717, 1559,

1453, 1404, 1319, 1159, 1072, 813, 665 cm^{-1}. HRMS (EI): Calculated for $C_{15}H_{16}NO_2S$ $(M-C_2H_3O)^+$ 274.0902, found 274.0913.

4-Phenyl-1-(tosylamino)butan-2-one (5f):

White semisolid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 2.42 (s, 3H), 2.66 (t, *J* = 7.5 Hz, 2H), 2.85 (t, *J* = 7.5 Hz, 2H) , 3.78 (d, *J* = 4.1 Hz, 2H), 5.25 (t, *J* = 4.1 Hz, 1H), 7.07-7.10 (m, 2H), 7.16-7.28 (m, 5H), 7.69-7.71 (m, 2H). ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ = 21.5, 29.4, 41.6, 51.6, 126.5, 127.1, 128.1, 128.6, 129.8, 134.1(?), 139.8, 143.8, 202.8.IR (neat) 3281, 3064, 3031, 2925, 2857, 1718, 1601, 1497, 1449, 1319, 1161, 1091, 815, 696 cm^{-1}. HRMS (EI): Calculated for $C_{13}H_{19}NO_3S$ $(M)^+$ 317.1086, found 317.1078.

3-Methyl-1-(tosylamino)butan-2-one (11a):

White solid. Mp 75-76ºC. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.02 (d, *J* = 7.1 Hz, 6H), 2.41 (s, 3H), 2.52 (sept, *J* = 7.1 Hz, 1H), 3.88 (d, *J* = 4.6 Hz, 2H), 5.30 (t, *J* = 4.6 Hz, 1H), 7.28-7.30 (m, 2H), 7.71-7.73 (m, 2H). ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ = 18.0, 21.5, 38.8, 49.4, 127.2, 129.7, 136.1, 143.8, 207.3. IR (neat) 3291, 3042, 2975, 2924, 2869, 1705, 1599, 1405, 1347, 1251, 1166, 1032, 808, 668 cm^{-1}. HRMS (EI): Calculated for $C_8H_{10}NO_2S$ $(M-C_4H_7O)^+$ 184.0432, found 184.0423.

1-Cyclohexyl-2 -(tosylamino)ethanone (11b):

White solid;. Mp 85-86 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.36 (m, 5H), 1.67 (m, 5H), 2.27 (m, 1H), 2.42 (s, 3H), 3.88 (d, *J* = 4.2 Hz, 2H), 5.36 (t, *J* = 4.2 Hz, 1H), 7.25-7.35 (m, 2H), 7.68-7.77 (m, 2H). ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ = 21.5, 25.3, 28.1, 48.4, 49.6, 127.2, 129.7, 136.0, 143.7, 206.5. IR (neat) 3285, 3042, 2939, 2921, 1717, 1598, 1455, 1411, 1321, 1167, 817, 710, 667 cm^{-1}. HRMS (EI): Calculated for $C_8H_{10}NO_2S$ $(M-C_7H_{11}O)^+$ 184.0432, found 184.0432.

Typical procedure (Table 2, entry 8): To TiI_4 (222 mg, 0.40 mmol) was added $TiCl_4$ (0.04 mL, 0.4 mmol) and CH_2Cl_2 (1.0 mL) at room temperature. The mixture was cooled to –78 ºC and to it was added a solution of (*S*)-2-isobutyl-*N*-*p*-tosylazetidin-3-one (**3e**) (56.2 mg, 0.20 mmol) in CH_2Cl_2 (1.0 mL) at –78 ºC. The resulting mixture was gradually warmed up to room temperature during 15 h and sat. aq. $NaHCO_3$, EtOAc (5.0 mL), and 10% aq. $NaHSO_3$ were added to quench the reaction. The mixture was filtrated through a Celite pad. The layers were separated and the aqueous layer was extracted with EtOAc (20 mL x 3). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give a crude product. Purification on silica gel TLC (*n*-hexane/CH_2Cl_2/Et_2O = 5/3/2) gave 5-methyl-1-(tosylamino)hexan-2-one (**5e**) (88%, 24.9 mg).

Reductive aldol reaction (Eq. 1): A solution of *N*-*p*-tosyl-2-ethylazetidin-3-one (**3c**) (50.6 mg, 0.20

mmol) in CH_2Cl_2 (1.0 mL) and a solution of chloral (58.8 mg, 0.40 mmol) in CH_2Cl_2 (1.0 mL) were added to a mixture of titanium tetraiodide (222.2 mg, 0.40 mmol) and indium trichloride (88.4 mg, 0.40 mmol) in CH_2Cl_2 (1.0 mL) at rt. The reaction mixture was stirred for 15 h. The reaction was quenched with sat. aq. $NaHCO_3$. The whole mixture was diluted with EtOAc (5.0 mL), followed by the addition of 10% aq.$NaHSO_3$. The mixture was filtered through a Celite pad. The layers were separated, and the aqueous layer was extracted with ethyl acetate (20 mL x 3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by preparative TLC on silica gel (developed once with *n*-hexane/CH_2Cl_2/Et_2O = 3/3/2) to give 1,1,1-trichloro-2-hydroxy-5-(tosylamino)heptan-4-one (**16**) (64.2 mg, 80%, *dr* = 80:20).

1,1,1-Trichloro-2-hydroxy-5-(tosylamino)heptan-4-one (16)- (upper):
White solid. Mp 111-112 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.90 (t, *J* = 7.3 Hz, 3H), 1.05 (d, *J* = 6.9 Hz, 3H), 2.13 (dsept, *J* = 3.7, 6.9 Hz, 1H), 2.39 (s, 3H), 2.57 (ddd, *J* = 1.8, 1.8, 17.4 Hz, 1H), 2.88 (dd, *J* = 9.2, 17.4 Hz, 1H), 3.12 (dd, *J* = 1.8, 4.6 Hz, 1H), 3.83 (dd, *J* = 3.7, 9.6 Hz, 1H), 4.40 (ddd, *J* = 1.8, 4.6, 9.2 Hz, 1H), 5.32 (d, *J* = 9.6 Hz, 1H), 7.26-7.29 (m, 2H), 7.68-7.71 (m, 2H). ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ = 16.1, 19.9, 21.5, 29.8, 42.9, 66.4, 78.2, 127.4, 129.8, 136.5, 143.9, 204.9. IR (neat) 3519, 3320, 3046, 2971, 1916, 1715, 1598, 1349, 1164, 1038, 673, 576 cm^{-1}. HRMS (EI): Calculated for $C_{10}H_{14}NO_2S$ $(M\text{-}C_4H_4Cl_3O_2)^+$ 212.0745, found 212.0765.

1,1,1-Trichloro-2-hydroxy-5-(tosylamino)heptan-4-one (16)- (lower):
White solid. Mp 111-112 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.90 (dd, *J* = 7.3, 7.3 Hz, 3H), 1.58 (ddq, *J* = 6.9, 7.3, 14.6 Hz, 1H), 1.87 (ddq, *J* = 4.6, 7.3, 14.6 Hz, 1H), 2.40 (s, 3H), 2.72 (ddd, *J* = 1.2, 2.3, 17.6 Hz, 1H), 2.88 (dd, *J* = 8.7, 17.6 Hz, 1H), 3.11 (dd, *J* = 1.2, 4.6 Hz, 1H), 3.93 (ddd, *J* = 4.6, 6.9, 8.0 Hz, 1H), 4.47 (ddd, *J* = 2.3, 4.6, 8.7 Hz, 1H), 5.35 (d, *J* = 8.0 Hz, 1H), 7.27-7.31 (m, 2H), 7.70-7.73 (m, 2H). ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ = 9.1, 21.5, 25.0, 42.2, 62.6, 78.3, 102.1, 127.3, 129.8, 136.7, 143.9, 204.8. IR (neat) 3471, 3255, 2969, 2928, 2885, 1719, 1598, 1293, 1167, 1091, 808, 664 cm^{-1}. HRMS (EI): Calculated for $C_{10}H_{14}NO_2S$ $(M\text{-}C_4H_4Cl_3O_2)^+$ 212.0745, found 212.0765.

Reductive aldol reaction (Eq. 2): To a mixture of TiI_4 (111 mg, 0.20 mmol), $TiCl_4$ (0.02 mL, 0.2 mmol), and $Pd(O_2CCF_3)_2$ (33.2 mg, 0.10 mmol) was added CH_2Cl_2 (1.0 mL) at rt. The mixture was cooled to 0 ºC and to it was added successively a solution of (*S*)-2-isobutyl-*N*-*p*-tosylazetidin-3-one (**3e**) (28.1 mg, 0.10 mmol) in CH_2Cl_2 (1.0 mL) and that of chloral (29.4 mg, 0.20 mmol) in CH_2Cl_2 (1.0 mL) at 0 ºC. The resulting mixture was gradually warmed up to room temperature during 15 h and sat. aq. $NaHCO_3$, EtOAc (5.0 mL), and 10% aq. $NaHSO_3$ were added successively to quench the reaction. The mixture was filtrated through a Celite pad. The layers were separated and the aqueous layer was extracted with EtOAc

(20 mL x 3). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give a crude product. Purification on silica gel TLC (*n*-hexane/CH_2Cl_2/Et_2O = 2/3/2, twice) gave (*R**)-3-((*R**)-2,2,2-trichloro-1-hydroxyethyl)-5-methyl- 1-(tosylamino)hexan-2-one (**18**) (28.5 mg, 66%).

(*R)-3-((*R**)-2,2,2-trichloro-1-hydroxyethyl)-5-methyl-1-(tosylamino)hexan-2-one (18):**
White solid. Mp 99-100 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.4 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 1.31-1.37 (m, 1H), 1.40-1.50 (m, 1H), 1.58-1.65 (m, 1H), 2.43 (s, 3H), 3.31 (ddd, *J* = 1.7, 6.3, 8.0 Hz, 1H), 3.98 (dd, *J* = 4.4, 20.0 Hz, 1H), 4.04 (dd, *J* = 4.4, 20.0 Hz, 1H), 4.11 (dd, *J* = 1.7, 9.0 Hz, 1H), 4.79 (d, *J* = 9.0 Hz, 1H), 5.28 (t, *J* = 4.4, Hz, 1H), 7.29-7.31 (m, 2H), 7.72-7.74 (m, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 21.5, 21.9, 22.5, 25.4, 40.0, 44.8, 52.8, 85.2, 102.4, 127.3, 129.8, 135.9, 144.1, 209.0. IR (KBr): 3478, 3278, 2933, 2870, 1703, 1321, 1166, 1096, 934, 809, 782, 662, 588 cm^{-1}. HRMS (EI): Calculated for $C_{16}H_{22}Cl_3NO_4S$ $(M)^+$ 429.0335, found 429.0346.

Typical procedure for the synthesis of azetidin-3-one *O*-alkyloximes: Pyridine (1.0 mL) was added to a solution of 2-methyl-1-tosylazetidin-3-one (**3b**) (837.5 mg, 3.5 mmol), *O*-methylhydroxylamine hydrochloride (584.6 mg, 7.0 mmol) and Na_2SO_4 (994.0 mg, 7.0 mmol) in CH_2Cl_2 (2.0 mL) at ambient temperature. The reaction mixture was stirring for 24 h. The reaction was quenched with H_2O. The whole mixture was diluted with EtOAc (15.0 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (20 mL x 3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified flash column chromatography (*n*-hexane/CH_2Cl_2/Et_2O = 4/3/2) to give 2-methyl-1-tosylazetidine-3-one *O*-methyloxime (**7a**) (911.0 mg, 97%, *E*:*Z* = 31:69).

2-Methyl-1-tosylazetidin-3-one *O*-methyloxime (7a):
97%, *E*:*Z* = 31:69. White solid. Mp 52-53 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.49 (d, *J* = 6.4 Hz, 2.07 H), 1.55 (d, *J* = 6.4 Hz, 0.93 H), 2.44 (s, 3H), 3.75 (s, 0.93 H), 3.77 (s, 2.07H), 4.23-4.27 (m, 1H), 4.41 (dd, *J* = 3.1, 13.7 Hz, 0.31H), 4.47 (dd, *J* = 3.7, 14.7 Hz, 0.69H), 4.66-4.73 (m, 1H), 7.34-7.36 (m, 2H), 7.71-7.74 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 18.1, 18.8, 21.6, 56.2, 56.7, 62.2, 62.3, 68.7, 69.3, 128.3, 128.4, 130.0, 131.9, 144.6, 148.7, 149.5. IR (neat): 2979, 2937, 2904, 2819, 1596, 1445, 1349, 1165, 1094, 1056, 1025, 977, 881, 818, 760, 710, 675, 626 cm^{-1}. HRMS (EI): Calculated for $C_{12}H_{16}N_2O_3S$ $(M)^+$ 268.0882, found 268.0870.

2-Ethyl-1-tosylazetidin-3-one *O*-methyloxime (7b):
98%, *E*:*Z* = 33:67. White solid. Mp 86-87 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00-1.04 (m, 3H),

1.83-1.90 (m, 2H), 2.44 (s, 3H), 3.75 (s, 0.99 H), 3.77 (s, 2.01H), 4.24-4.28 (m, 1H), 4.41 (dd, *J* = 3.7, 14.2 Hz, 0.33H), 4.43 (dd, *J* = 3.7, 15.1 Hz, 0.67H), 4.59-4.64 (m, 0.67H), 4.72-4.76 (m, 0.33H), 7.34-7.36 (m, 2H), 7.71-7.73 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 8.6, 8.7, 21.6, 24.4, 26.2, 56.6, 56.9, 62.2, 62.3, 73.8, 74.6, 128.3, 128.3, 129.9, 132.0, 144.5, 147.5, 148.9. IR (neat): cm^{-1} 2971, 2939, 2879, 2820, 1597, 1458, 1350, 1165, 1094, 1037, 885, 817, 711, 674, 619, 581. HRMS (EI): Calculated for $C_{13}H_{18}N_2O_3S$ $(M)^+$ 282.1038, found 282.1032.

2-Isobutyl-1-tosylazetidin-3-one *O*-methyloxime (7c):

96%, *E*:*Z* = 30:70. White solid. Mp 84-85 ºC.^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90-0.96 (m, 6H), 1.69-1.82 (m, 2H), 1.86-2.00 (m, 1H), 2.44 (s, 3H), 3.75 (s, 0.90H), 3.76 (s, 2.10H), 4.27 (dd, *J* = 1.8, 15.1 Hz, 0.70H), 4.29 (dd, *J* = 1.4, 14.2 Hz, 0.30H), 4.42 (dd, *J* = 3.7, 14.2 Hz, 0.30H), 4.29 (dd, *J* = 3.7, 15.1 Hz, 0.70H), 4.64-4.69 (m, 0.70H), 4.71-4.74 (m, 0.30H), 7.35-7.37 (m, 2H), 7.71-7.73 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 21.6, 22.5, 22.7, 23.1, 24.2, 24.3, 40.6, 42.5, 56.6, 56.8, 62.3, 71.4, 72.3, 128.3, 128.4, 129.9, 131.9, 132.1, 144.5, 144.5, 148.5, 149.6. IR (neat): cm^{-1} 2958, 2871, 2819, 1596, 1559, 1465, 1352, 1165, 1093, 1038, 886, 817, 710, 677, 617, 577. HRMS (EI): Calculated for $C_{15}H_{22}N_2O_3S$ $(M)^+$ 310.1351, found 310.1339.

The yield of **7d** was 84%. **(*E*)-7d** was 15%. **(*Z*)-7d** was 69%. *E*:*Z* = 18:82.

(*E*)-2-Isopropyl-1-tosylazetidin-3-one *O*-methyloxime [(*E*)-7d]:

Colorless semisolid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.03 (d, *J* = 6.9 Hz, 3H), 1.03 (d, *J* = 7.3 Hz, 3H), 2.22-2.29 (m, 1H), 2.44 (s, 3H), 3.75 (s, 3H), 4.29 (dd, *J* = 1.3, 14.2 Hz, 1H), 4.34 (dd, *J* = 3.2, 14.2 Hz, 1H), 4.64-4.66 (m, 1H), 7.34-7.36 (m, 2H), 7.71-7.73 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 17.6, 18.2, 21.6, 30.2, 57.1, 62.2, 79.5, 128.3, 129.9, 132.4, 144.4, 147.2. IR (neat): 2966, 2937, 2898, 2876, 2819, 1598, 1463, 1351, 1165, 1093, 1046, 880, 818, 711, 676, 626, 600 cm^{-1}. HRMS (EI): Calculated for $C_{14}H_{20}N_2O_3S$ $(M)^+$ 296.1195, found 296.1196.

(*Z*)-2-Isopropyl-1-tosylazetidin-3-one *O*-methyloxime [(*Z*)-7d]:

White solid. Mp 54-55 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (d, *J* = 6.9 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 2.02-2.10 (m, 1H), 2.41 (s, 3H), 3.74 (s, 3H), 4.26 (dd, *J* = 1.4, 15.1 Hz, 1H), 4.36 (dd, *J* = 3.7, 15.1 Hz, 1H), 4.48-4.50 (m, 1H), 7.32-7.34 (m, 2H), 7.69-7.71 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 16.9, 18.0, 21.5, 31.5, 57.0, 62.2, 77.9, 128.3, 129.9, 132.2, 144.4, 148.3. IR (neat): 2966, 2938, 2901, 2877, 2819, 1598, 1495, 1466, 1389, 1351, 1165, 1094, 1046, 882, 817, 711, 690, 661, 597 cm^{-1}. HRMS (EI): Calculated for $C_{14}H_{20}N_2O_3S$ $(M)^+$ 296.1195, found 296.1189.

The yield of **7e** was 98%. **(*E*)-7e** was 27%. **(*Z*)-7e** was 71%. *E*:*Z* = 28:72.

(*E*)-2-Isopropyl-1-tosylazetidin-3-one *O*-*tert*-butyloxime [(*E*)-7e]:

White solid. Mp 106-107 ºC. δ = 1.03 (d, *J* = 6.9 Hz, 3H), 1.04 (d, *J* = 6.8 Hz, 3H), 1.17 (s, 9H), 2.21-2.29 (m, 1H), 2.44 (s, 3H), 4.30 (dd, *J* = 1.9, 14.2 Hz, 1H), 4.35 (dd, *J* = 3.2, 15.1 Hz, 1H), 4.63-4.65 (m, 1H), 7.34-7.36 (m, 2H), 7.72-7.74 (m, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 17.8, 18.0, 21.6, 27.3, 30.3, 57.4, 79.3, 79.7, 128.3, 129.9, 132.6, 144.2, 145.3. IR (neat): 2974, 2928, 2873, 1559, 1507, 1455, 1367, 1348, 1188, 1163, 1100, 1033, 945, 818, 710, 677, 612 cm^{-1}. HRMS (EI): Calculated for $C_{17}H_{26}N_2O_3S$ $(M)^+$ 338.1664, found 338.1663.

(*Z*)-2-Isopropyl-1-tosylazetidin-3-one *O*-*tert*-butyloxime [(*Z*)-7e]:

White solid. Mp 73-74 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (d, *J* = 6.9 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 1.17 (s, 9H), 2.03-2.14 (m, 1H), 2.43 (s, 3H), 4.26 (dd, *J* = 1.0, 14.6 Hz, 1H), 4.37 (dd, *J* = 3.2, 14.6 Hz, 1H), 4.53-4.55 (m, 1H), 7.33-7.35 (m, 2H), 7.72-7.74 (m, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 16.8, 18.2, 21.6, 27.2, 31.5, 57.3, 78.1, 79.0, 128.3, 129.8, 132.5, 144.2, 146.5. IR (neat): 2973, 2929, 2876, 1560, 1507, 1458, 1354, 1164, 1094, 1021, 952, 815, 710, 680, 600 cm^{-1}. HRMS (EI): Calculated for $C_{17}H_{26}N_2O_3S$ $(M)^+$ 338.1664, found 338.1655.

The yield of **7f** was 94%. **(*E*)-7f** was 21%. **(*Z*)-7f** was 73%. *E*:*Z* = 22:78.

(*E*)-2-Isopropyl-1-tosylazetidin-3-one *O*-isopropyloxime [(*E*)-7f]:

White solid. Mp 56-57 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.03 (d, *J* = 5.0 Hz, 3H), 1.05 (d, *J* = 5.0 Hz, 3H), 1.12 (d, *J* = 6.4 Hz, 3H), 1.15 (d, *J* = 6.4 Hz, 3H), 2.22-2.30 (m, 1H), 2.44 (s, 3H), 4.19 (sept, *J* = 6.4 Hz, 1H), 4.29 (dd, *J* = 1.8, 14.2 Hz, 1H), 4.35 (dd, *J* = 3.7, 14.2 Hz, 1H), 4.63-4.65 (m, 1H), 7.34-7.36 (m, 2H), 7.72-7.74 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 17.8, 18.0, 21.3, 21.5, 21.6, 30.2, 57.3, 76.2, 79.6, 128.3, 129.9, 132.5, 144.3, 146.1. IR (neat): 2972, 2932, 2875, 1598, 1455, 1352, 1166, 1118, 1093, 1016, 970, 816, 710, 674, 660, 616 cm^{-1}. HRMS (EI): Calculated for $C_{16}H_{24}N_2O_3S$ $(M)^+$ 324.1508, found 324.1505.

(*Z*)-2-Isopropyl-1-tosylazetidin-3-one *O*-isopropyloxime [(*Z*)-7f]:

White solid. Mp 68-69 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01 (d, *J* = 6.9 Hz, 3H), 1.03 (d, *J* = 6.9 Hz, 3H), 1.10 (d, *J* = 6.4 Hz, 3H), 1.13 (d, *J* = 6.0 Hz, 3H), 2.03-2.13 (m, 1H), 2.42 (s, 3H), 4.19 (sept, *J* = 6.4 Hz, 1H), 4.27 (dd, *J* = 1.8, 15.1 Hz, 1H), 4.36 (dd, *J* = 3.7, 15.1 Hz, 1H), 4.50-4.53 (m, 1H), 7.32-7.34 (m, 2H), 7.70-7.72 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 16.9, 18.1, 21.2, 21.4, 21.5, 31.5, 57.3, 75.9, 78.0, 128.3, 129.8, 132.4, 144.3, 147.4. IR (neat): 2973, 2931, 2876, 1599, 1496, 1467, 1350, 1164, 1115, 1018, 966, 891, 849, 817, 710, 685, 660, 600 cm^{-1}. HRMS (EI): Calculated for $C_{16}H_{24}N_2O_3S$ $(M)^+$ 324.1508, found 324.1499.

Typical procedure (Table 5, entry 4)

A solution of (*Z*)-2-isopropyl-1-tosylazetidin-3-one *O*-isopropyloxime [**(*Z*)-7f**] (32.4 mg, 0.10 mmol) in CH_2Cl_2 (1.0 mL) was added to a solution of titanium tetrabromide (55.1 mg, 0.15 mmol) in CH_2Cl_2 (1.0 mL) at 0°C. The reaction mixture was allowed to warm to ambient temperature with stirring for 5 h. The reaction was quenched with sat. aq. $NaHCO_3$. The whole mixture was diluted with EtOAc (5.0 mL). The mixture was filtered through a Celite pad. The layers were separated, and the aqueous layer was extracted with ethyl acetate (20 mL x 3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by preparative TLC on silica gel (*n*-hexane/CH_2Cl_2/Et_2O = 4/3/2) to give the mixture of (*Z*)- and (*E*)-3-bromo-4-methyl-1-(tosylamino)pentan-2-ones [**(*E*)-** and **(*Z*)-8f-Br**] (31.2 mg, 77%, *E*/*Z* = 97:3).

(*E*)-3-Chloro-1-(tosylamino)butan-2-one *O*-methyloxime [(*E*)-8a-Cl]:

Colorless semisolid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.59 (d, *J* = 6.9 Hz, 3H), 2.43 (s, 3H), 3.67 (dd, *J* = 6.4, 15.1 Hz, 1H), 3.85 (s, 3H), 3.92 (dd, *J* = 7.3, 15.1 Hz, 1H), 4.62 (q, *J* = 6.9 Hz, 1H), 5.19-5.22 (m, 1H), 7.31-7.33 (m, 2H), 7.73-7.76 (m, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 21.3, 21.5, 38.4, 55.8, 62.5, 127.1, 129.8, 136.5, 143.8, 154.2. IR (neat): 3289, 2981, 2939, 2901, 2873, 2820, 1598, 1494, 1443, 1331, 1219, 1162, 1093, 1042, 997, 907, 815, 667 cm^{-1}. HRMS (EI): Calculated for $C_{12}H_{17}ClN_2O_3S$ $(M)^+$ 304.0648, found 304.0644.

(*Z*)-3-Chloro-1-(tosylamino)butan-2-one *O*-methyloxime [(*Z*)-8a-Cl]:

Colorless semisolid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 (d, *J* = 6.9 Hz, 3H), 2.42 (s, 3H), 3.81 (s, 3H), 3.87 (dd, *J* = 6.0, 16.5 Hz, 1H), 3.94 (dd, *J* = 4.6, 16.5 Hz, 1H), 5.12-5.14 (m, 1H), 5.23 (q, *J* = 6.9 Hz, 1H), 7.29-7.31 (m, 2H), 7.74-7.77 (m, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 21.5, 21.7, 41.4, 47.9, 62.5, 127.3, 129.7, 136.4, 143.7, 152.3. IR (neat): 3287, 2979, 2938, 2901, 2873, 2823, 1598, 1493, 1444, 1332, 1229, 1163, 1094, 1043, 909, 814, 666 cm^{-1}. HRMS (EI): Calculated for $C_{12}H_{17}ClN_2O_3S$ $(M)^+$ 304.0648, found 304.0655.

(*E*)-3-Bromo-1-(tosylamino)butan-2-one *O*-methyloxime [(*E*)-8a-Br]:

Colorless semisolid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.76 (d, *J* = 6.9 Hz, 3H), 2.44 (s, 3H), 3.67 (dd, *J* = 6.4, 15.1 Hz, 1H), 3.86 (s, 3H), 3.96 (dd, *J* = 7.4, 15.1 Hz, 1H), 4.71 (q, *J* = 6.9 Hz, 1H), 5.27-5.30 (m, 1H), 7.32-7.34 (m, 2H), 7.74-7.76 (m, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 21.5, 21.9, 39.2, 46.2, 62.5, 127.1, 129.8, 136.5, 143.8, 154.7. IR (neat): 3290, 2977, 2938, 2821, 1598, 1494, 1442, 1331, 1162, 1092, 1041, 991, 815, 669 cm^{-1}. HRMS (EI): Calculated for $C_{12}H_{17}BrN_2O_3S$ $(M)^+$ 348.0143, found 348.0131.

(*Z*)-3-Bromo-1-(tosylamino)butan-2-one *O*-methyloxime [(*Z*)-8a-Br]:

Colorless semisolid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.65 (d, *J* = 6.9 Hz, 3H), 2.43 (s, 3H), 3.83 (s, 3H), 3.89 (dd, *J* = 5.9, 16.5 Hz, 1H), 3.99 (dd, *J* = 5.0, 16.5 Hz, 1H), 5.11-5.14 (m, 1H), 5.26 (q, *J* = 6.9 Hz, 1H), 7.30-7.32 (m, 2H), 7.76-7.78 (m, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 21.5, 22.0, 35.3, 41.6, 62.6, 127.3, 129.7, 136.4, 143.6, 152.0. IR (neat): 3286, 2972, 2937, 2867, 2821, 1598, 1442, 1332, 1162, 1093, 1598, 1442, 1332, 1162, 1093, 1047, 910, 813, 666 cm^{-1}. HRMS (EI): Calculated for $C_{12}H_{17}BrN_2O_3S$ $(M)^+$ 348.0143, found 348.0129.

(*E*)-3-Bromo-4-methyl-1-(tosylamino)pentan-2-one *O*-methyloxime [(*E*)-8d-Br]:

White solid. Mp 107-108 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (d, *J* = 6.9 Hz, 3H), 1.13 (d, *J* = 6.4 Hz, 3H), 2.11-2.20 (m, 1H), 2.44 (s, 3H), 3.65 (dd, *J* = 5.5, 14.2 Hz, 1H), 3.82-3.88 [m, 4H, including a singlet of O*CH*$_3$ at δ = 3.85 (3H)], 4.25 (d, *J* = 9.6 Hz, 1H), 5.24-5.27 (m, 1H), 7.32-7.34 (m, 2H), 7.75-7.78 (m, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 20.6, 21.3, 21.5, 32.6, 39.0, 60.6, 62.6, 127.2, 129.8, 136.4, 143.8, 153.9. IR (neat): 3272, 2968, 2937, 2871, 2822, 1595, 1493, 1457, 1410, 1334, 1210, 1164, 1094, 1047, 998, 908, 865, 835, 819, 663, 607 cm^{-1}. HRMS (EI): Calculated for $C_{14}H_{21}BrN_2O_3S$ $(M\text{-}Br)^+$ 297.1273, found 297.1261.

(*Z*)-1-Bromo-4-methyl-3-(tosylamino)pentan-2-one *O*-methyloxime [(*Z*)-8d-Br]:

Colorless semisolid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.81 (d, *J* = 6.4 Hz, 3H), 1.07 (d, *J* = 6.4 Hz, 3H), 1.89-1.99 (m, 1H), 2.43 (s, 3H), 3.82 (dd, *J* = 5.9, 16.4 Hz, 1H), 3.82 (s, 3H), 4.04 (dd, *J* = 4.5, 16.4 Hz, 1H), 4.88 (d, *J* = 10.0 Hz, 1H), 5.19-5.21 (m, 1H), 7.29-7.31 (m, 2H), 7.76-7.78 (m, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 19.5, 21.1, 21.5, 32.3, 42.1, 49.2, 62.5, 127.3, 129.7, 136.4, 143.6, 151.3. IR (neat): 3287, 2967, 2936, 2873, 2821, 1598, 1494, 1460, 1334, 1162, 1093, 1050, 910, 868, 815, 706, 668 cm^{-1}. HRMS (EI): Calculated for $C_{14}H_{21}N_2O_3S$ $(M\text{-}Br)^+$ 297.1273, found 297.1273.

(*E*)-3-Bromo-4-methyl-1-(tosylamino)pentan-2-one *O*-*tert*-butyloxime [(*E*)-8e-Br]:

Colorless semisolid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (d, *J* = 6.4 Hz, 3H), 1.13 (d, *J* = 6.9 Hz, 3H), 1.24 (s, 9H), 2.10-2.19 (m, 1H), 2.44 (s, 3H), 3.61 (dd, *J* = 5.5, 13.7 Hz, 1H), 3.84 (dd, *J* = 7.8, 13.7 Hz, 1H), 4.30 (d, *J* = 9.1 Hz, 1H) 5.27-5.30 (m, 1H), 7.32-7.34 (m, 2H), 7.74-7.77 (m, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 20.5, 21.3, 21.5, 27.4, 32.5, 39.4, 61.5, 80.5, 127.2, 129.8, 136.3, 143.7, 152.2. IR (neat): 3289, 2977, 2930, 2873, 1597, 1453, 1411, 1388, 1366, 1331, 1261, 1164, 1118, 1093, 975, 858, 813, 667 cm^{-1}. HRMS (EI): Calculated for $C_{13}H_{19}N_2O_3S$ $(M\text{-}C_4H_8Br)^+$ 283.1116, found 283.1107.

(*E*)-3-Bromo-4-methyl-1-(tosylamino)pentan-2-one *O*-isopropyloxime [(*E*)-8f-Br]:

White solid. Mp 59-60 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 6.9 Hz, 3H), 1.11 (d, *J* = 6.4 Hz,

3H), 1.18 (d, *J* = 6.4 Hz, 3H), 1.20 (d, *J* = 6.4 Hz, 3H), 2.07-2.18 (m, 1H), 2.43 (s, 3H), 3.61 (dd, *J* = 5.0, 13.7 Hz, 1H), 3.82 (dd, *J* = 8.3, 13.7 Hz, 1H), 4.25-4.34 (m, 2H), 5.25 (dd, *J* = 5.0, 8.2 Hz, 1H), 7.31-7.36 (m, 2H), 7.72-7.76 (m, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 20.6, 21.3, 21.5, 32.5, 39.2, 61.1, 76.9, 127.2, 129.8, 136.2, 143.7, 153.0. IR (neat): 3290, 2975, 2930, 2873, 1456, 1330, 1164, 1118, 1094, 977, 815, 668 cm^{-1}. HRMS (EI): Calculated for $C_{16}H_{25}N_2O_3S$ $(M\text{-}Br)^+$ 325.1586, found 325.1580.

(*Z*)-3-Bromo-4-methyl-1-(tosylamino)pentan-2-one *O*-isopropyloxime [(*Z*)-8f-Br]:

Colorless semisolid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.78 (d, *J* = 6.9 Hz, 3H), 1.05 (d, *J* = 6.4 Hz, 3H), 1.17 (d, *J* = 6.4 Hz, 3H), 1.17 (d, *J* = 6.4 Hz, 3H), 1.89-1.98 (m, 1H), 2.40 (s, 3H), 3.80 (dd, *J* = 5.9, 16. 5 Hz, 1H), 4.03 (dd, *J* = 4.6, 16. 5 Hz, 1H), 4.26 (sept, *J* = 6.4 Hz, 1H), 4.89 (d, *J* = 10.1 Hz, 1H), 5.23-5.26 (m, 1H), 7.27-7.29 (m, 2H), 7.74-7.76 (m, 2H).^{13}C NMR (126 MHz, $CDCl_3$): δ = 19.4, 21.1, 21.4, 21.4, 21.5, 32.5, 42.2, 49.7, 76.8, 127.2, 129.7, 136.4, 143.5, 150.3. IR (neat): 3284, 2974, 2930, 2873, 1598, 1457, 1335, 1163, 1119, 1094, 1006, 872, 814, 669 cm^{-1}. HRMS (EI): Calculated for $C_{16}H_{25}N_2O_3S$ $(M\text{-}Br)^+$ 325.1586, found 325.1592.

Typical procedure (Table 6, entry 4)

A solution of 2-isobutyl-1-tosylazetidin-3-one (**3e**) (28.1 mg, 0.10 mmol) in CH_2Cl_2 (1.0 mL) was added to a solution of titanium tetrabromide (73.5 mg, 0.20 mmol) in CH_2Cl_2 (1.0 mL) at 0 ºC. The reaction mixture was allowed to warm to ambient temperature with stirring for 17 h. The reaction was quenched with sat. aq. $NaHCO_3$. The whole mixture was diluted with EtOAc (5.0 mL). The mixture was filtered through a Celite pad. The layers were separated, and the aqueous layer was extracted with ethyl acetate (20 mL x 3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by preparative TLC on silica gel (*n*-hexane/CH_2Cl_2/Et_2O = 4/3/2) to give 1-bromo-5-methyl-3-(tosylamino)hexan-2-one (**6e**) (32.2 mg, 89%).

1-Bromo-3-(tosylamino)butan-2-one (6b):

Colorless semisolid.^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (d, *J* = 6.3 Hz, 3H), 2.41 (s, 3H), 3.90 (d, *J* = 13.3 Hz, 1H), 3.99 (d, *J* = 13.3 Hz, 1H), 4.24-4.31 (m, 1H), 5.34 (d, *J* = 7.4 Hz, 1H), 7.29-7.31 (m, 2H), 7.71-7.73 (m, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 19.0, 21.5, 30.7, 55.1, 127.1, 129.9, 136.5, 144.1, 200.4. IR (neat): 3264, 2930, 1730, 1597, 1495, 1422, 1332, 1160, 1093, 1035, 955, 875, 814, 667 cm^{-1}. HRMS (EI): Calculated for $C_9H_{12}NO_2S$ $(M\text{-}C_2H_2BrO)^+$ 198.0589, found 198.0586.

1-Bromo-3-(tosylamino)pentan-2-one (6c):

Colorless semisolid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 7.3 Hz, 3H), 1.52-1.63 (m, 1H),

1.81-1.91 (m, 1H), 2.42 (s, 3H), 3.84 (d, *J* = 13.2 Hz, 1H), 3.93 (d, *J* = 13.2 Hz, 1H), 4.18-4.23 (m, 1H), 5.39 (d, *J* = 8.3 Hz, 1H), 7.29-7.31 (m, 2H), 7.71-7.73 (m, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 9.3, 21.5, 25.8, 31.1, 60.4, 127.2, 129.8, 136.4, 144.0, 200.2. IR (neat): 3276, 2973, 2937, 2879, 1730, 1598, 1494, 1424, 1334, 1163, 1091, 1050, 1009, 908, 813, 773, 670, 570 cm^{-1}. HRMS (EI): Calculated for $C_{12}H_{16}BrNO_3S$ $(M)^+$ 333.0034, found 333.0036.

1-Bromo-4-methyl-3-(tosylamino)pentan-2-one (6d):

Colorless semisolid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.74 (d, *J* = 6.9 Hz, 3H), 1.03 (d, *J* = 6.9 Hz, 3H), 2.07-2.15 (m, 1H), 2.41 (s, 3H), 3.78 (d, *J* = 13.2 Hz, 1H), 3.83 (d, *J* = 13.2 Hz, 1H), 4.16 (dd, *J* = 5.1, 9.2 Hz, 1H), 5.36 (d, *J* = 9.2 Hz, 1H), 7.28-7.30 (m, 2H), 7.69-7.71 (m, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 16.3, 19.7, 21.5, 30.4, 31.7, 64.2, 127.3, 129.7, 136.3, 143.9, 200.2. IR (neat): 3250, 2965, 2931, 2901, 2873, 1742, 1647, 1447, 1394, 1325, 1168, 1092, 1029, 876, 812, 682, 584 cm^{-1}. HRMS (EI): Calculated for $C_{11}H_{16}NO_2S$ $(M\text{-}C_2H_2BrO)^+$ 226.0902, found 226.0902.

1-Bromo-5-methyl-3-(tosylamino)hexan-2-one (6e):

Colorless semisolid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.78 (d, *J* = 6.4 Hz, 3H), 0.84 (d, *J* = 6.9 Hz, 3H), 1.29-1.51 (m, 2H), 1.67-1.76 (m, 1H), 2.40 (s, 3H), 3.85 (d, *J* = 13.2 Hz, 1H), 3.94 (d, *J* = 13.2 Hz, 1H), 4.16-4.22 (m, 1H), 5.40 (d, *J* = 8.7 Hz, 1H), 7.27-7.29 (m, 2H), 7.70-7.72 (m, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 21.0, 21.5, 23.0, 24.4, 31.4, 41.3, 57.9, 127.3, 129.8, 136.2, 144.0, 201.0. IR (neat): 3281, 2959, 2871, 1732, 1598, 1494, 1421, 1335, 1162, 1092, 961, 926, 815, 706, 669 cm^{-1}. HRMS (EI): Calculated for $C_{12}H_{18}NO_2S$ $(M\text{-}C_2H_2BrO)^+$ 240.1058, found 240.1052.

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