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# REGIOSELECTIVE RING-OPENING REACTION OF 2-MONO-SUBSTITUTED AZETIDIN-3-ONES PROMOTED BY THE COMBINED USE OF TITANIUM TETRAIODIDE AND ITS CHLORO OR BROMO COUNTERPART

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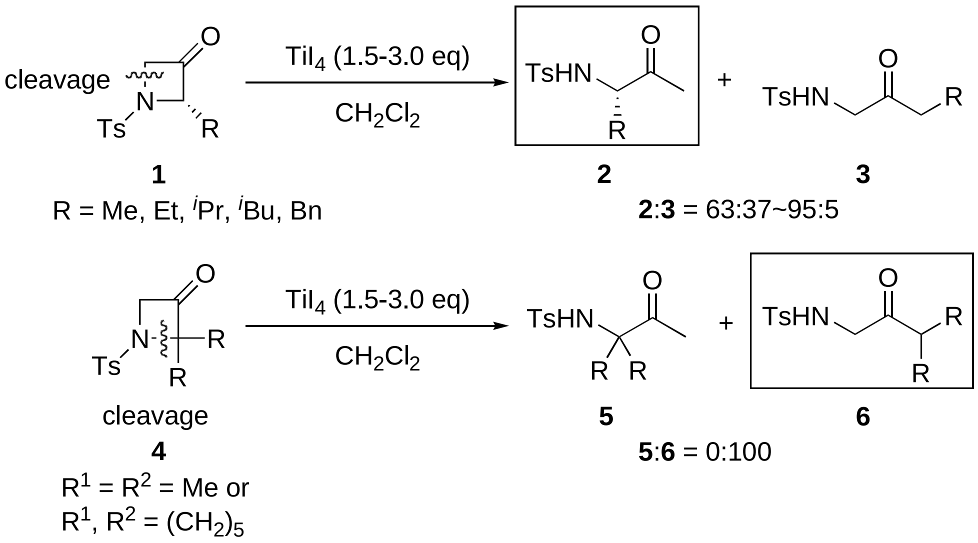
This paper is dedicated to Professor Albert Padwa on the occasion of his 75th birthday.

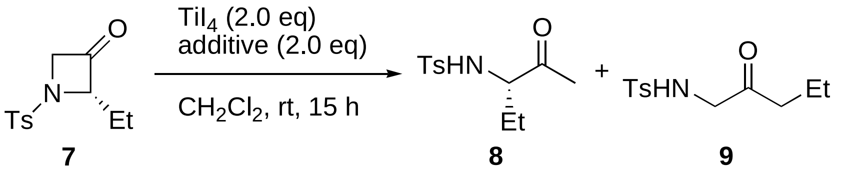
**Abstract** – The ring-opening reaction of 2-mono-substituted azetidin-3-ones at the more substituted bond occurred with the combined use of $TiI_4$ and $TiCl_4$ to give the corresponding ketones in moderate to high yields with high regioselectivity. The reductive aldol reaction of the enolate thus prepared proceeded with chloral in the presence of $Pd(O_2CCF_3)_2$ to give the *syn*-aldol adduct in moderate yield.

Azetidines are four-membered cycles including one nitrogen atom. Among them, most representative derivatives are azetidin-2-ones such as penicillin, cepharosporin, and thienamycin, etc. On the other hand, azetidin-3-ones have not been well studied because azetidin-3-ones do not exist in nature. However, azetidin-3-ones are proposed as intermediates for the synthesis of natural products or biologically active compounds containing an azetidine ring.[1,2] We have reported titanium tetraiodide promoted aldol and Mannich-type reactions by the reductive generation of enolates *via* ring-opening of aziridines bearing carbonyl groups such as alkoxycarbonyls or keto carbonyls to give adducts in good to excellent yields.[3] Aza-aldol reaction has also been reported using reductive ring-opening of 2-(1-benzyloxyiminoethyl)-aziridine to afford $\alpha$-aminomethyl-$\beta$-hydroxy ketone *O*-alkyl oximes in good to high yields with *anti*-selectivities.[4] In these reactions, it is crucial that the regioselective ring opening reaction of aziridines followed by reductive enolate formations, which are regarded as $\beta$-amino carbonyl compounds synthons. We next examined the reaction of azetidin-3-ones with $TiI_4$ and found that the enolates were readily prepared followed by the subsequent aldol or Mannich-type reactions.[5] In the reductive ring-opening reaction of 2-mono-substituted azetidin-3-ones, C-N bond cleavages occurred at the less sterically congested bond to give the ketone **2** preferentially. On the other hand, C-N bond cleavages of 2,2-disubstituted azetidin-3-ones proceeded at the more substituted bond to afford the only ketone **6** (Scheme 1). Regarding the different regioselectivity, we proposed two different pathways including $S_N2$-like process by $TiI_4$ or a one-electron transfer promoted by low-valent titanium species, which were in situ generated *via* the disproportion of $TiI_4$. In order to realize the ring-opening reaction of 2-mono-substituted azetidin-3-ones at the more substituted bond, several conditions were examined. Herein, we describe regioselective ring-opening of 2-mono-substituted azetidin-3-ones with a combined use of $TiI_4$ and titanium chloride or bromide.



**Scheme 1.** Regioselective Ring-opening of Azetidin-3-ones Using $TiI_4$

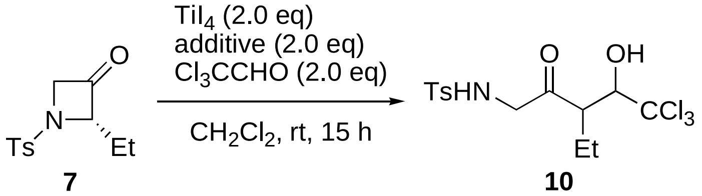
**Table 1**. Effects of Additives



| Entry | Additive | Yield (%)[a] | **8**:**9**[b] | Entry | Additive | Yield (%)[a] | **8**:**9**[b] |
|---|---|---|---|---|---|---|---|
| 1 | none | 66 | 83:17 | 6 | $AlI_3$ | 57 | 74:26 |
| 2 | Al powder | 29 | 4:96 | 7 | $AlBr_3$ | 60 | 5:95 |
| 3 | DIBAL | 0 | – | 8 | $AlCl_3$ | 51 | 5:95 |
| 4 | $LiAlH_4$ | 31 | 87:13 | 9 | $Et_2AlCl$ | 45 | 70:30 |
| 5 | Zn/Cu | 87 | 85:15 | 10 | $EtAlCl_2$ | 76 | 14:86 |

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

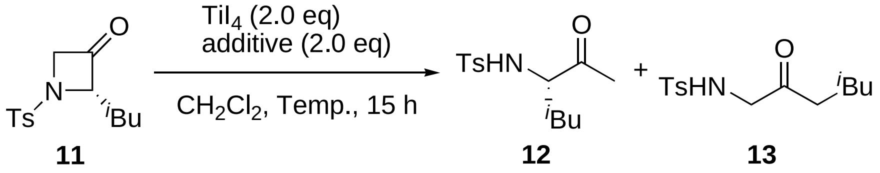
First, effects of additives to reduce $TiI_4$ to low-valent titanium species were examined in the model reaction of 2-mono-substituted azetidin-3-one **7**, which is the most suitable substrate for the reductive aldol reaction.[5] Although among them, Al powder was effective for the regioselectivity, the yield was low (entries 1-5 in Table 1). We next investigated several aluminum reagents. When $AlBr_3$, $AlCl_3$, and $EtAlCl_2$ were used, ketone **9** was obtained in moderate yield with good regioselectivity (entries 6-10).[6] The reductive aldol reaction of azetidin-3-one **7** with chloral was carried out with a combined use of $TiI_4$ and $AlBr_3$, $AlCl_3$, or $EtAlCl_2$. No desired aldol adduct **10** was obtained, and instead, those reactions gave ketones **8** and **9** or complex mixtures (Eq. 1).



(1)

Effects of other additives were investigated in the reaction of 2-mono-substituted azetidin-3-one **11**. Table 2 summarizes the results. Among additives tested at room temperature, $TiBr_4$ and $TiCl_4$ were found to be efficient in both yields and regioselectivities (entries 5 and 6). The ring-opening reaction of **11** with a combined use of $TiI_4$ and $TiBr_4$ or $TiCl_4$ at lower temperatures gave the desired ketone in high yields with good to high selectivities (entries 7 and 8).[7]

**Table 2.** Effects of Additives

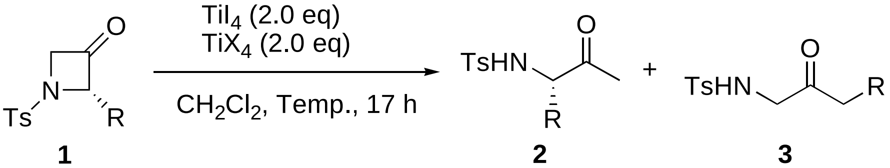


| Entry | Additive | Temp. | Yield (%)[a] | **12**:**13**[b] |
|---|---|---|---|---|
| 1 | none | 0 °C to rt | 97 | 63:37 |
| 2 | $^{i}Pr_3SiOTf$ | rt | 43 | 17:83 |
| 3 | $Ti(O^{i}Pr)_4$ | rt | complex mixture | – |
| 4 | $Cp_2TiCl_2$ | rt | 43 | 11:89 |
| 5 | $TiBr_4$ | rt | 72 | 26:74 |
| 6 | $TiCl_4$ | rt | 61 | 9:91 |
| 7 | $TiBr_4$ | –20 to 10 °C | 90 | 16:84 |
| 8 | $TiCl_4$ | –78 °C to rt | 88 | 0:100 |

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

The reductive ring-opening reactions of several 2-mono-substituted azetidin-3-ones **1** were examined using $TiI_4$-$TiBr_4$ or $TiCl_4$. Table 3 summarizes the results. When $TiBr_4$ was used as an additive, the reductive ring-opening reaction of several 2-mono-substituted azetidin-3-ones regioselectively proceeded to give ketones in low to moderate yields (entries 1-3). Yields were improved using $TiCl_4$ as an additive to give ketones in moderate to high yields with high regioselectivities (entries 4-6).

**Table 3.** Reductive Ring-opening Reaction of Several 2-Mono-substituted Azetidin-3-ones

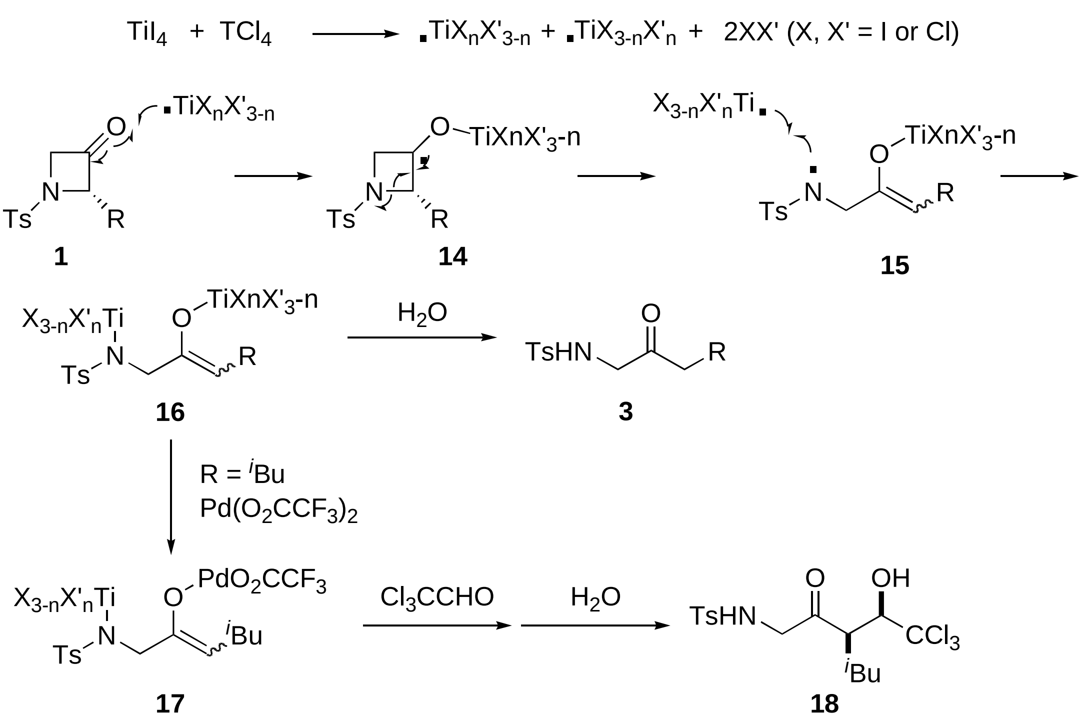


| Entry | R | X | Temp. | Yield (%)[a] | **2**:**3**[b] |
|---|---|---|---|---|---|
| 1 | Me | Br | –78 °C to rt | 26 | 25:75 |
| 2 | Et | Br | –78 °C to rt | 30 | 4:96 |
| 3 | $^i$Pr | Br | –78 °C to rt | 56 | 0:100 |
| 4 | Me | Cl | 0 °C to rt | 63 | 9:91 |
| 5 | Et | Cl | 0 °C to rt | 78 | 4:96 |
| 6[c] | $^i$Pr | Cl | –20 to 10 °C | 84 | 0:100 |

[a]Each regioisomer was not separated. [b]Ratios were determined by $^1$H NMR spectra. [c]The reaction was carried out for 21 h.

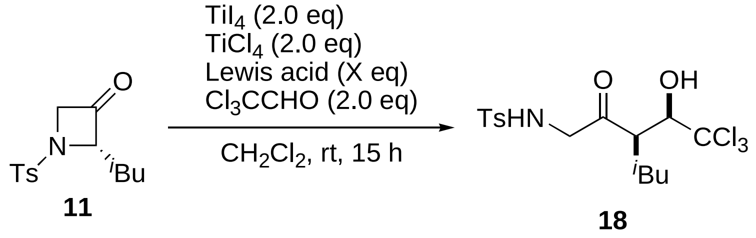
A plausible reaction mechanism is shown in Scheme 2. The disproportion of titanium tetraiodide and tetrachloride gives low-valent titanium species. A one-electron transfer to 2-mono-substituted azetidin-3-one **1** at the C-3 position gives a radical intermediate **14**. The ring-opening reaction of **14** would proceed by fragmentation at the N-C(2) bond to give the more substituted titanium enolate **16**, which is more stable than the less substituted one, and the subsequent protonation with water to quench the reaction would give the corresponding ketone **3**.

Finally, we examined the reductive aldol reaction of the more substituted titanium enolate generated in situ with an aldehyde. The reaction of 2-mono-substituted azetidin-3-one **11** with chloral was carried out using $TiI_4$-$TiCl_4$ to give the aldol adduct **18** in 24% yield along with the reduction product **13** in 64% yields (Table 4, entry 1). To improve the yield, several Lewis acids were investigated as an additive (entries 2-7). Among metal salts examined, $PdCl_2$ was slightly effective, and therefore, several palladium salts were examined (entries 8-12). As a result, $Pd(O_2CCF_3)_2$ was found to be the most effective to give the aldol adduct in 66% yield with *syn*-selectivity.[8] 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 **17**, which would be responsible for the improvement of the yield under the present conditions.



**Scheme 2.** Plausible Reaction Mechanism

**Table 4.** Reductive Aldol Reaction of 2-Mono-substituted Azetidin-3-one **11**



| Entry | Lewis acid (eq) | Yield (%)[a] | Entry | Lewis acid (eq) | Yield (%)[a] |
|---|---|---|---|---|---|
| 1 | none | 24 | 7 | $PdCl_2$ (1.0) | 27 |
| 2 | $InCl_3$ (2.0) | 11 | 8 | $PdCl_2(CH_3CN)_2$ (1.0) | 16 |
| 3 | $ZnCl_2$ (2.0) | 13 | 9 | $PdCl_2(PPh_3)_2$ (1.0) | 27 |
| 4 | $FeCl_3$ (2.0) | 9 | 10 | $Pd(OAc)_2$ (1.0) | 30 |
| 5 | $ZrCl_4$ (2.0) | 13 | 11[b] | $Pd(OAc)_2$ (1.0) | 47 |
| 6 | $Eu(fod)_3$ (2.0) | 0 | 12[b] | $Pd(O_2CCF_3)_2$ (1.0) | 66 (64)[c] |

[a] Isolated yield. [b] The reaction was carried out at 0 °C to room temperature. [c] $Pd(O_2CCF_3)_2$ (0.50 eq) was used.

In conclusion, we found that the ring-opening reaction of 2-mono-substituted azetidin-3-ones occurred at the more substituted bonds using $TiI_4$-$TiCl_4$ to give the corresponding ketones in moderate to high yields with high regioselectivity and also that the subsequent reductive aldol reaction with chloral proceeded in the presence of $Pd(O_2CCF_3)_2$ to give the *syn*-aldol adduct in moderate yield.

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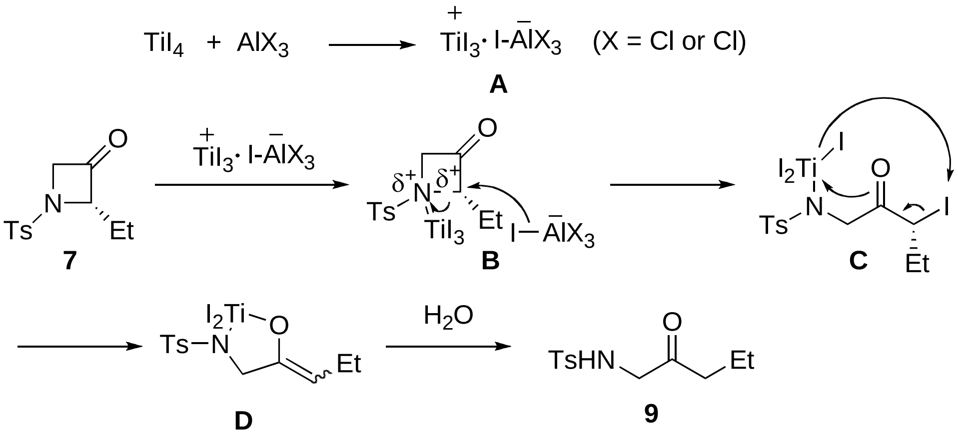
6.



**Scheme 3.** Plausible Reaction Mechanism

Although the roles of $AlCl_3$, $AlBr_3$, and $EtAlCl_2$ are not yet clear, we presume a mechanism as shown in Scheme 3. First, the reaction of $TiI_4$ with aluminum salts may produce a more Lewis acidic titanium species **A**, which in turn activates the tosylamide nitrogen. An $S_N2$-like reaction occurs at the carbon having a partially positive charge to generate the iodo ketone **C** and the subsequent reaction with another iodide anion effects formation of a titanium enolate species **D**, and the protonation with water to quench the reaction would give ketone **9**. On the other hand, $AlI_3$ and $Et_2AlCl$ were not effective because they are less Lewis acidic compared to the above aluminum salts and would not generate any complex like **A**.

7. **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 °C and to it was added a solution of (*S*)-2-isobutyl-*N*-*p*-tosylazetidin-3-one (**11**) (56.2 mg, 0.20 mmol) in $CH_2Cl_2$ (1.0 mL) at –78 °C. 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 (**13**) (24.9 mg, 88%). White solid. Mp 82-83 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 0.83 (d, *J* = 6.4 Hz, 6H), 1.34-1.49 (m, 3H), 2.33 (t, *J* = 7.8 Hz, 2H), 2.42 (s, 3H), 3.83 (d, *J* = 4.5 Hz, 2H), 5.39 (t, *J* = 4.5 Hz, 1H), 7.28-7.31 (m, 2H), 7.72-7.75 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 21.5, 22.1, 27.5, 32.2, 38.1, 51.2, 127.2, 129.7, 136.0, 143.7, 204.0. IR (KBr): 3464, 2953, 2871, 1719, 1495, 1467, 1405, 1370, 1346, 1323, 1159, 1119, 1092, 1064, 1019, 849, 812, 674 cm$^{-1}$. HRMS (EI): Calcd for $C_{14}H_{21}NO_3S$ $(M)^+$ 283.1242, found 283.1246.
8. **Typical procedure (Table 4, entry 12):** 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 room temperature. The mixture was cooled to 0 °C and to it was added successively a solution of (*S*)-2-isobutyl-*N*-*p*-tosylazetidin-3-one (**11**) (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 °C. 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%). White solid. Mp 99-100 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 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 MHz, $CDCl_3$): $\delta$ = 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): Calcd for $C_{16}H_{22}Cl_3NO_4S$ $(M)^+$ 429.0335, found 429.0346.