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Reductive Aldol and Mannich-Type Reactions of Azetidin-3-ones Promoted by Titanium Tetraiodide

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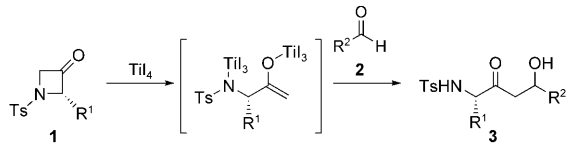
Dedicated to the 150th anniversary of Japan–UK diplomatic relations

1,4- and 1,3-Amino alcohols and diamines are widely used as synthons and other fine chemicals.[1] Consequently, the search for reliable methodologies for the construction of such building blocks in a regio- and stereoselective manner has received considerable attention. The most straightforward synthetic approach involves the use of aldol and Mannich-type reactions. However, there are some drawbacks associated with the enolate formations. As the conventional preparations of enolates involve deprotonation of the parent carbonyl compounds, there are some problems regarding the regioselectivity on the deprotonation of unsymmetrically substituted ketones. This problem on regiochemistry has recently been circumvented by utilizing the Rh- or Ir-catalyzed hydrogenation of unsaturated ketones.[2] Regarding this regiochemical issue, we have recently found that titanium tetraiodide generates enolate derivatives by the reduction of α-haloketones in a regioselective fashion.[3,4]

The applicability of the titanium tetraiodide-mediated system would be greatly enhanced with more conventional methods, avoiding the troubles caused by the use of α-haloketones, for example, instability and tedious preparation. These drawbacks led us to direct our studies toward the use of fused heterocyclic substrates.[5] First, the 2-acylaziridines were used as substrates, which would provide the latent α-haloketones by the reductive approach with titanium tetraiodide. As a result, the aldol or Mannich-type products were obtained by the treatment of 2-acetyl- or methoxycarbonyl-*N*-tosylaziridine derivatives with titanium tetraiodide followed by the addition of aldehydes or imines.[6]

There are only a few reports available for the regioselective C–C bond formation using the enolate from aminoacetone derivatives.[7] Therefore, the application of our methodology to this subject would lead to a straightforward procedure. Azetidin-3-one was chosen as a suitable precursor to the enolate because of the ring-strain derived from its small ring (Scheme 1). This paper describes a convenient method for the generation and reaction of the enolates of aminoacetone equivalents, which uses the reduction of azetidin-3-one with titanium tetraiodide and subsequent reactions with electrophiles. We utilized azetidine-3-ones, which were prepared easily from various α-amino acids.[8]



Scheme 1. The present strategy for the formation and reaction of enolate.

We initially examined the reducing ability of titanium tetraiodide using azetidin-3-one **1**. Treatment of azetidin-3-one with TiI_4 (1.5 eq) in EtCN at −78 °C to room temperature for 22.5 h cleanly gave the amino ketone **4** in moderate yield as shown in Table 1 (Entry 1). The influence of several *N*-protecting groups was next examined under various conditions. Table 1 summarizes the results. The best result was obtained by using *p*-tosylazetidin-3-one (*p*-Ts) as a protecting group in CH_2Cl_2 at 0 °C to room temperature (Entry 3). Titanium tetraiodide recorded a good result for generating the enolates efficiently from azetidin-3-one derivatives, whereas the use of other metal halides (MgI_2,[9a,b] AlI_3, ZnI_2[5i], $TiCl_4$[9c–e]) did not give satisfactory results. The effect of the protecting group is important. The ring-opening reaction of the azetidin-3-one (R = Bn) did not take place with a weak electron-donating substituent.

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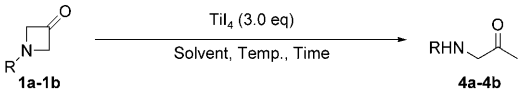
Table 1. Titanium tetraiodide-promoted ring-opening reaction of azetidin-3-ones.

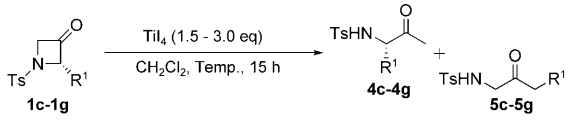


Entry	R	Solvent	T [°C]	t [h]	Yield [%]
1	Ts	EtCN	−78°C to RT	22.5	43
2	Ts	CH_2Cl_2	−78°C to RT	20	63
3[a]	Ts	CH_2Cl_2	0°C to RT	15	80
4[b]	Ts	DME	−78°C to RT	18	35
5	Cbz	EtCN	−78°C to RT	13.5	24
6	Cbz	CH_2Cl_2	−78°C to RT	8	trace

[a] TiI_4 (1.5 eq) was used. [b] TiI_4 (6.0 eq) was used.

Further studies were carried out to examine the regioselectivity of the reductive ring-opening reaction. Reductive ring-opening of various 2-substituted azetidin-3-ones is summarized in Table 2. The reduction of azetidin-3-ones derived

Table 2. Regioselectivity of the reductive ring-opening reaction of various 2-substituted azetidin-3-ones.



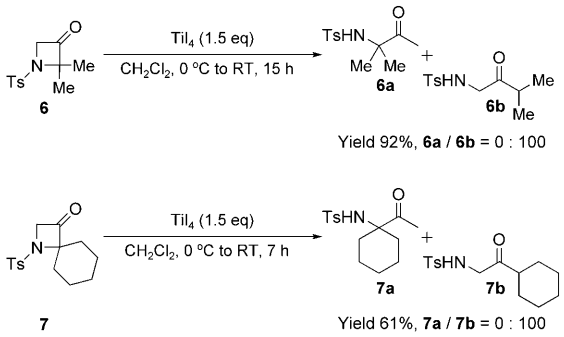
Entry	R^1	TiI_4[Eq]	T [°C]	Yield [%][a]	**4**:**5**
1	Me	2.0	0°C to RT	89	95:5
2	Et	1.5	RT	66	83:17
3	*i*Pr	3.0	RT	76	77:23
4	*i*Bu	2.0	0°C to RT	97	63:37
5	Bn	3.0	RT	82	92:8

[a] Each regioisomer was not separated.

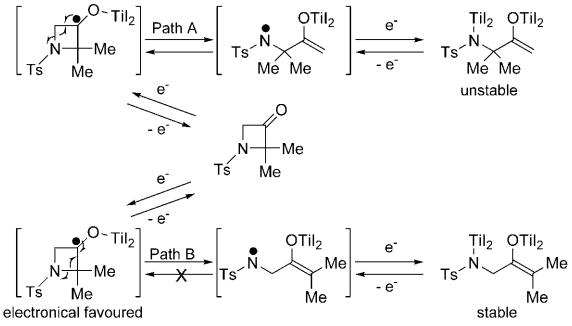
from various α-amino acids gave mixtures of amino ketones **4** and **5** in moderate to good yields with good to high regioselectivities, in which the steric congestion at C-2 of the azetidine ring affected the regioselectivity. Unfortunately, racemization of amino ketones **4** was observed to some extent during the enolate formation.

The results of the reductive ring-opening reaction with 2,2-disubstituted azetidin-3-one are shown in Scheme 2. Complete regioselectivity was observed on the reductive ring-opening of 2,2-dimethyl-substituted azetidin-3-one. The use of spirohexyl azetidin-3-one, a more sterically congested substrate, also recorded high regioselectivity albeit in a decreased yield of the product. Regioselectivity of the reductive ring-opening reaction is controlled by electronic factors as well as steric effects of the 2-substitution.

Although more detailed examinations appear to be needed, at present we propose a plausible mechanism shown in Scheme 3. The reduction of azetidin-3-one would proceed though in two different pathways, and it seems that an electron-transfer reaction would play a significant role. Initially, the disproportion of titanium tetraiodide gives low-valent titanium species. One electron transfer to azetidin-3-



Scheme 2. The regioselectivity on the ring-opening reaction of 2,2-disubstituted azetidin-3-one.



Scheme 3. An explanation for the complete regioselectivity of the reductive ring-opening reaction of 2,2-dimethyl-azetidin-3-one.

one at the C-3 position gives a radical intermediate. A ring-opening reaction proceeded by fragmentation at the N−C(2) or N−C(4) bond. At this point, fragmentation at N−C(2) bond was favored because of the electronically stabilized 2,2-dimethyl substitution. Further reduction of azetidine leads to the corresponding titanium enolate. Also, the homolysis of N−C(4) bond gives the less substituted enolate (path A). Alternatively, the homolysis of N−C(2) bond leads to the more substituted enolate (path B). In path A, the enolate could reverse to the azetidine by re-cyclization under the equilibrium. However, path B may not involve such a cyclization because of the steric hindrance. Finally, the more thermodynamically stable enolate would predominate. The examination into a more precise mechanism is still underway.

The reductive aldol reaction of azetidin-3-ones with aldehydes was next examined, and Table 3 summarizes the results. Unfortunately, treatment of azetidin-3-one **1a** (R^1 = H) with benzaldehyde in the presence of TiI_4 gave a trace amount of the desired 1,4-amino alcohol **3a** (R^1 = H, R^2 = Ph) along with the aminoacetone derivative **4a** (R^1 = H) in 78% yield (Entry 1). Low Lewis acidity of titanium tetraiodide might be responsible for this result.

To improve the yield, the addition of various Lewis acids was investigated. The presence of $TiCl_4$ and $InCl_3$ were found to be effective. When $TiCl_4$ was used as an additive, the desired aldol adduct **3a** (R^1 = H, R^2 = Ph) was obtained in 12% yield (Entry 2). The use of chloral as a reactive alde-

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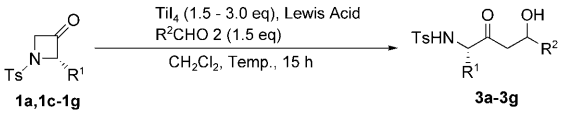
Table 3. Reductive aldol reaction of azetidin-3-ones.[a]

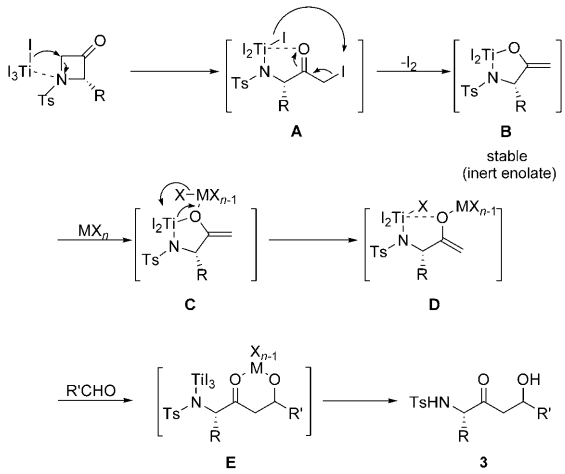


Entry	R^1	R^2	TiI_4 [Eq]	L.A.	*T* [°C]	Yield [%][b]	*dr*
1	H	Ph	3.0	None	0°C to RT	Trace (78)	–
2	H	Ph	1.5	$TiCl_4$, 1.5	0°C to RT	12 (61)	–
3	H	CCl_3	1.5	$TiCl_4$, 1.5	0°C to RT	41 (17)	–
4	Me	CCl_3	1.5	$TiCl_4$, 1.5	0°C to RT	11 (53)	50:50
5	Me	CCl_3	1.5	$InCl_3$, 1.5	0°C to RT	33 (34)	50:50
6	Me	CCl_3	2.0	$InCl_3$, 2.0	0°C to RT	46 (30)	50:50
7	Me	CCl_3	2.0	$InCl_3$, 2.0	RT	57 (30)	50:50
8[c]	Me	CCl_3	2.0	$InCl_3$, 2.0	RT	70 (30)	68:32
9	Me	CCl_3	3.0	$InCl_3$, 3.0	RT	55 (30)	50:50
10	Me	CCl_3	2.0	$InBr_3$, 2.0	RT	41 (55)	50:50
11	Me	CCl_3	2.0	InI_3, 2.0	RT	30 (0)	50:50
12	Et	CCl_3	2.0	$InCl_3$, 2.0	RT	51(49)	83:17
13[c]	Et	CCl_3	2.0	$InCl_3$, 2.0	RT	80(10)	80:20
14[c]	*i*Pr	CCl_3	2.0	$InCl_3$, 2.0	RT	28(26)	84:16
15[d]	*i*Pr	CCl_3	2.0	None	0°C to RT	43(35)	81:19
16[d]	Bn	CCl_3	2.0	None	0°C to RT	41(31)	63:37

[a] Reactions were performed with azetidin-3-one (0.10 mmol) in CH_2Cl_2 (3.0 mL), unless otherwise indicated. [b] Yields of the reduction products are in parentheses. [c] Reactions were performed with azetidin-3-one (0.20 mmol), chloral (0.40 mmol), TiI_4 (0.40 mmol), and $InCl_3$ (0.40 mmol) in CH_2Cl_2 (2.0 mL). [d] Reactions were performed with azetidin-3-one (0.20 mmol), chloral (0.40 mmol), TiI_4 (0.40 mmol), and $InCl_3$ (0.40 mmol) in CH_2Cl_2 (2.5 mL).

hyde was next examined. The reaction of azetidine-3-one **1a** (R^1=H) with chloral gave the adduct **3b** (R^1=H, R^2=CCl_3) in moderate yield (Entry 3). On the other hand, the aldol reaction of **1c** (R^1=Me) derived from L-alanine with chloral in the presence of a mixture of TiI_4–$TiCl_4$ (each 1.5 equiv to **1c**) gave the adduct **3c** (R^1=Me, R^2=CCl_3) in 11% yield (Entry 4). When $InCl_3$ was used in place of $TiCl_4$ as an additive, the adduct **3c** (R^1=Me, R^2=CCl_3) was obtained in 33% yield (Entry 5). To improve the yield, the reaction conditions were investigated regarding the indium species, amounts of TiI_4 and InX_3, and reaction temperatures (Entries 6–11). The reaction of **1c** (R^1=Me) with chloral in the presence of a mixture of TiI_4–$InCl_3$ (each 2.0 equiv to **1c**) gave the aldol adduct **3c** in 57% yield (Entry 7). Also, an increase in the concentration of the reaction improved the product yield (Entry 8). The aldol reaction of **1d** (R^1=Et) with chloral in the presence of a mixture of TiI_4–$InCl_3$ (each 2.0 equiv to **1d**) gave the adduct **3d** (R^1=Et, R^2=CCl_3) in 51% yield (Entry 12). The increased yield of the adduct **3d** (80% yield) was obtained when a three-fold concentration of substrate **1d** (R^1=Et) was examined in the presence of a mixture of TiI_4–$InCl_3$ (each 2.0 equiv to **1d**). The aldol reaction of **1e** (R^1=*i*Pr) derived from L-valine with chloral in the presence of a mixture of TiI_4–$InCl_3$ (2.0 equiv each) gave the adduct **3e** (R^1=*i*Pr, R^2=CCl_3) in 28% yield (Entry 14). The aldol adduct **3e** (R^1=*i*Pr, R^2=CCl_3) was obtained in 43% yield without the added Lewis acids (Entry 14). To investigate the scope of electrophiles, 3-chlorobenzaldehyde was used in the presence of $ZnCl_2$ as an additive. The desired product (R^1=*i*Pr, R^2=3-ClC_6H_4) was formed along with the dehydration product in 57% combined yield. The reaction of **1g** (R^1=Bn) derived from L-phenylalanine with chloral gave the aldol adduct **3g** (R^1=Bn, R^2=CCl_3) in 41% yield (Entry 16).

Although there is much room for the examination of the regioselectivity, one plausible explanation is shown in Scheme 4. In the case of mono-substituted azetidin-3-ones,



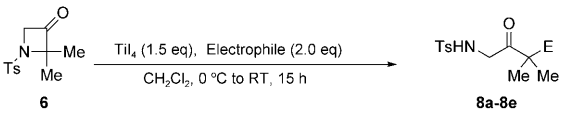
Scheme 4. Plausible reaction mechanism.

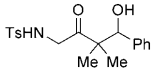
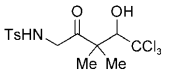
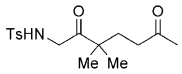
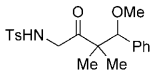
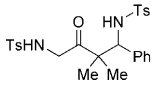
the reaction would prefer an S_N2-like process rather than one electron transfer, because radical stabilization is more depressed compared with that of 2,2-disubstituted cases. Initially, α-iodoketone A is generated by the ring-opening of azetidin-3-one. The formation of intermediary α-iodoketones and the reductive formation of enolates have been precedented.[3,6] At this point, attack at the less hindered site by the iodide anion was favored. The requirement for an additional Lewis acid may be explained by the formation of a more reactive enolate D from the stable titania cycle B. Finally, the aldol reaction with aldehyde furnishes the product **3**. We next examined the reductive C–C bond-forming reaction with 2,2-dimethyl-substituted azetidin-3-one and various electrophiles (Table 4).

In contrast to monosubstituted azetidin-3-ones, chloral was not a good electrophile. Among the other electrophiles (MVK, acetal) tested, *N*-tosylimine derived from benzaldehyde afforded a Mannich-type adduct in moderate yield (Entry 5).

In conclusion, we found that the enolates from aminoacetone derivatives were readily prepared using the reduction of azetidin-3-ones with titanium tetraiodide, and that subsequent C–C bond formation with aldehyde or imine proceeded in poor to good yields. This methodology provides a straightforward access to 1,4-amino alcohols or diamines in a regioselective manner.

Table 4. Reductive C–C bond-forming reaction with various electrophiles.



Entry	Electrophile	Product	Yield [%]
1			0
2[a]			9[a]
3			0
4			0
5			52

[a] Decomposition involving a retro-aldol reaction was observed on TLC.

Experimental Section

A typical experimental procedure (Table 3, entry 7): A solution of *N*-*p*-tosyl-2-methylazetidin-3-one **1c** (23.9 mg, 0.10 mmol) in CH_2Cl_2 (1.0 mL) and a solution of chloral (22.1 mg, 0.15 mmol) in CH_2Cl_2 (1.0 mL) were added successively to a mixture of titanium tetraiodide (111.1 mg, 0.20 mmol) and indium trichloride (44.2 mg, 0.20 mmol) in CH_2Cl_2 (1.0 mL) at room temperature. After the mixture was stirred for 15 h, it was quenched with a saturated aqueous solution of $NaHCO_3$. The whole mixture was diluted with AcOEt, followed by the addition of an aqueous solution of $NaHSO_3$ (10%). The mixture was filtered through a celite pad. The layers were separated, and the aqueous layer was extracted with ethyl acetate (10 mL×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 twice with *n*-hexane/CH_2Cl_2/Et_2O=5:3:2 and then twice with CH_2Cl_2) to give 5,5,5-trichloro-4-hydroxy-1-(*p*-tosylamino)-pentan-2-one **3c** (57%, 22.1 mg).

Acknowledgements

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Keywords: aldol reaction · homogeneous catalysis · ketones · reduction · regioselectivity

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