

Titanium Tetraiodide-Promoted Reductive Enolate Formation of α -Tosyloxy Ketone Derivatives and Aldol Reaction with Aldehydes

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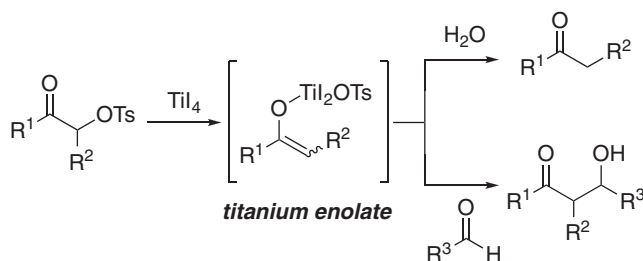
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Titanium tetraiodide-promoted reductive enolate formation from α -tosyloxy ketone derivatives and subsequent aldol reaction of the resulting enolates with aldehydes gave β -hydroxy ketones.

Reduction of α -oxygenated ketone derivatives has been recognized as an important synthetic transformation and applied to the synthesis of biologically active compounds. A variety of methods for these reductions have been reported to date. Metals such as zinc,¹ samarium,² and chromium³ have been used as representative reducing reagents.⁴ In these reactions, metal enolates or anion species are generated as intermediates and subsequently protonated with a protic solvent to give the corresponding ketones. Among them, samarium diiodide (SmI_2) is widely used for the synthesis of multifunctionalized compounds due to good chemoselectivity. Takeuchi and Mikami reported SmI_2 -mediated enolate formation of α -alkoxy ketone in an aprotic solvent such as THF followed by enantioselective protonation using a chiral diol as a proton source.⁵ There are only a few reports using electrophiles other than a proton. Lin reported SmI_2 -promoted electrophilic amination of ketone enolates derived from α -methoxyalkanones with di-*tert*-butyl azodicarboxylate in THF to give useful α -aminated ketones.⁶ Lin has also examined SmI_2 -promoted aldol reaction of the enolate derived from 2-methoxycycloalkanones with aldehydes. However, in place of β -hydroxy ketones, 1,3-diols are provided as a result of subsequent Evans–Tishchenko reaction probably due to the formation of the samarium alkoxide intermediate activated for another equivalent of aldehydes.⁷ The ability of titanium tetraiodide (TiI_4) to reduce various organic molecules has been investigated in our group and titanium tetraiodide-promoted reactions including reductive aldol and Mannich-type reactions have been reported.⁸ This paper describes the titanium enolates formation by reducing α -tosyloxy ketone derivatives with TiI_4 in an aprotic solvent and subsequent aldol reaction of the enolates with aldehydes (Scheme 1).

The effects of substituents in the oxygenated ketone derivatives and solvents were examined. Table 1 summarizes



Scheme 1. TiI_4 -promoted reductive enolate formation of α -alkoxy ketone derivatives and aldol reaction with aldehydes.

Table 1. Deoxygenation of α -Oxygenated Ketone Derivatives

Entry	R ¹	R ²	R ³	1	Solvent	Time/h	2 (Yield/%) ^a
1	Ph	H	Bn	1a	EtCN	1.5	2a (0 ^b)
2	4-MeC ₆ H ₄	H	Ac	1b	EtCN	17	2b (74)
3	4-MeC ₆ H ₄	H	Bz	1c	EtCN	17	2b (74)
4	4-MeC ₆ H ₄	H	Ts	1d	EtCN	1.5	2b (80)
5	Ph	Me	Ms	1e	EtCN	13	2c (80)
6	Ph	Me	Ts	1f	EtCN	16	2c (85)
7	Ph	Me	Ts	1f	ClCH_2CN	2	2c (35, 70 ^c)
8	Ph	Me	Ts	1f	CH_2Cl_2	3	2c (17)
9	Ph	Me	Ts	1f	THF	20	2c (65)
10	Ph	Me	Ts	1f	toluene	7	2c (75)

a) Isolated yields. b) α -Hydroxyacetophenone was obtained in 71% yield. c) The reaction was carried out in the presence of salicylic acid (1 equiv) as an additive for 1 h.

the results. When the reaction of α -benzyloxyacetophenone (**1a**) was carried out with TiI_4 in EtCN, debenzoylation proceeded to give α -hydroxyacetophenone in 71% yield (Entry 1). We next examined ketones bearing AcO, BzO, TsO, and MsO groups whose leaving abilities are higher than that of the benzyloxy group. As a result, reduction of α -acyloxy ketones **1b** and **1c** (Entries 2 and 3) and sulfonyloxy ketones **1d–1f** (Entries 4–6) gave the desired ketones **2b** or **2c** in moderate to good yields. The reaction of tosyloxy ketone **1f** in ClCH_2CN gave a complex mixture and the yield of the desired ketone **2c** decreased. When salicylic acid was added as an additive, ketone **2c** was obtained in 70% yield (Entry 7).^{8a,9} The reaction in THF or toluene gave ketone **2c** in 65% and 75% yields, respectively (Entries 9 and 10).

We next examined TiI_4 -promoted reductive aldol reaction of α -tosyloxypropionophenone (**1f**) with benzaldehyde in EtCN. However, no desired aldol adduct was obtained, and instead, a reduction product, ketone **2c** was obtained in 54% yield. In order to obtain the desired aldol adduct, several reaction conditions such as solvents, equivalents of TiI_4 , α -tosyloxypropionophenone (**1f**), and benzaldehyde were investigated. When the reduction of α -tosyloxypropionophenone (**1f**) (1.5 equiv) was carried out using TiI_4 (3.0 equiv) in ClCH_2CN followed by the addition of a solution of benzaldehyde in $\text{C}_6\text{H}_5\text{Cl}$, the desired

Table 2. Reductive Aldol Reaction of α -Tosyloxy Ketone Derivatives

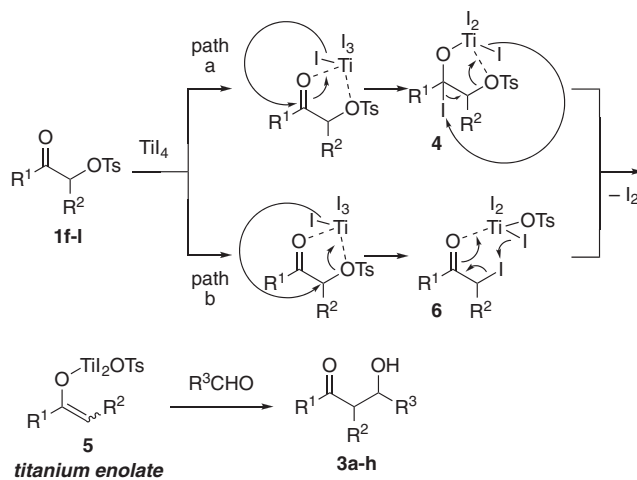
$ \begin{array}{c} \text{R}^1 \\ \\ \text{C}=\text{O} \\ \\ \text{R}^2-\text{C}-\text{OTs} \\ \text{1f-l} \\ (1.5 \text{ equiv}) \end{array} \xrightarrow[\text{ClCH}_2\text{CN, rt, time}]{\text{TiI}_4 (3 \text{ equiv})} \xrightarrow[\text{C}_6\text{H}_5\text{Cl, rt, 1 h}]{\text{R}^3\text{CHO}} \begin{array}{c} \text{R}^1 \\ \\ \text{C}=\text{O} \\ \\ \text{R}^2-\text{C}-\text{CH}(\text{OH})-\text{R}^3 \\ \text{3a-h} \end{array} $							
Entry	R ¹	R ²	1	R ³	Time	3	Yield/% (<i>syn:anti</i>) ^{a)}
1	Ph	Me	1f	Ph	2 h	3a	92 (85:15)
2	Ph	ⁱ Pr	1g	Ph	1 h	3b	66 (32:68) ^{b)}
3	Ph	Ph	1h	Ph	5 min	3c	36 (46:54)
4	^t Bu	Me	1i	Ph	2 h	3d	58 (96:4) ^{b)}
5	Cy	Me	1j	Ph	2 h	3e	33 (51:49) ^{b)}
6	2-furyl	Me	1k	Ph	2 h	3f	52 (63:37)
7	Ph	Me	1f	Cy	2 h	3g	28 (50:50)
8	Ph	Me	1f	^t Bu	2 h	—	—
9	Ph	H	1l	Ph	— ^{c)}	3h	14 ^{d)}

a) Isolated yields. b) Diastereomeric ratios were determined by ¹H NMR spectra. c) A mixture of ketone **1l** and benzaldehyde in CICH₂CN was added to a solution of TiI₄ in CICH₂CN. d) (*E*)-1,3-Diphenylprop-2-en-1-one was obtained in 66% yield.

aldol adduct **3a** was obtained in 92% yield with good *syn*-selectivity (Table 2, Entry 1). The results under the optimized reaction conditions are shown in Table 2. Use of acetophenone derivatives having bulky substituents such as ⁱPr and Ph decreased both yields and diastereoselectivity (Entries 2 and 3). The reaction of *tert*-butyl ketone gave the adduct **3d** in moderate yield with high *syn*-selectivity (Entry 4). The use of heteroaromatic ketone such as 2-furyl ketone gave the adduct **3f** in moderate yield (Entry 6). The present reductive aldol reaction is sensitive to the steric bulk of the aldehyde. The reaction of cyclohexanecarbaldehyde gave the adduct **3g** in 28% yield (Entry 7). On the other hand, the reaction using pivalaldehyde gave no aldol adduct (Entry 8). Although the reaction of α -tosyloxyacetophenone (**1l**) (R¹ = Ph, R² = H) with benzaldehyde proceeded, the corresponding aldol adduct **3h** was obtained in 14% yield along with dehydrated (*E*)-1,3-diphenylprop-2-en-1-one in 66% yield as a major product (Entry 9).

Scheme 2 shows possible reaction pathways. The present reaction appears to involve an initial attack of iodide anion at the carbonyl carbon to give the intermediate **4** and subsequent reaction with another iodide anion effects formation of the titanium enolate species **5** (path a) or replacement of the tosyloxy group with iodide anion forms α -iodo ketone **6** and subsequently another iodide anion attacks the iodine to generate the titanium enolate species **5** (path b). The enolate thus generated reacts with aldehyde to give the corresponding β -hydroxy ketone **3a–3h**.

In conclusion, we have found that the titanium enolate formation by reducing α -tosyloxy ketone derivatives with TiI₄ and aldol reactions of the enolates with aldehydes proceeds to give β -hydroxy ketones. Since titanium tetraiodide is commercially available and inexpensive, the present reaction offers an

**Scheme 2.** Possible mechanisms for the enolate formation.

alternative method for the reduction of α -oxygenated ketone derivatives and their reaction.

Experimental

General. Infrared spectra were recorded on a JASCO FT/IR-460 Plus spectrometer. ¹H NMR spectra were recorded on a JEOL JNM α -500 spectrometer (500 MHz) with tetramethylsilane as an internal standard. ¹³C NMR spectra were recorded on a JEOL JNM α -500 spectrometer (126 MHz). Chemical shifts are reported in δ units, parts per million from the central peak of CDCl₃ (δ 77.0) as an internal reference. High-resolution mass spectra (EI) were recorded on a JEOL JMS-700D mass spectrometer. Propionitrile (EtCN) and chloroacetone (ClCH₂CN) were distilled from P₂O₅ and then from CaH₂, and stored over molecular sieves 4A. Dichloromethane (CH₂Cl₂) was predried with P₂O₅, distilled from CaH₂, and stored over molecular sieves 4A. THF was distilled from benzophenone ketyl immediately before use. Toluene was predried with CaCl₂, distilled, 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.

Synthesis of α -Alkoxy, Acyloxy, and Sulfonyloxy Ketone Derivatives 1a–1l. α -Oxygenated ketone derivatives **1a**,¹⁰ **1b** and **1c**,¹¹ and **1d–1l**¹² were prepared according to literature methods.

A Typical Experimental Procedure for the Deoxygenation of α -Oxygenated Ketone Derivatives is as Follows (Table 1, Entry 6). To a solution of TiI₄ (166.6 mg, 0.30 mmol) in EtCN (1.0 mL) was added a solution α -tosyloxypropionophenone (**1f**) (45.7 mg, 0.15 mmol) in EtCN (1.0 mL) at room temperature under an argon atmosphere. The mixture was stirred at room temperature for 16 h and then quenched with saturated aqueous NaHCO₃, and EtOAc and 10% aqueous NaHSO₃ were added successively. The mixture was filtered through a Celite pad, and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by preparative silica gel TLC (hexane–EtOAc = 4:1 as an eluent)

to give propiophenone (**2c**) (17.0 mg, 85%) and the recovered α -tosyloxypropiophenone (**1f**) (5.6 mg, 12%), respectively.

Propiophenone (2c): Colorless oil; $^1\text{H NMR}$ (500 MHz, CDCl_3): δ 1.22 (t, $J = 7.3$ Hz, 3H), 2.99 (q, $J = 7.3$ Hz, 2H), 7.42–7.46 (m, 2H), 7.52–7.55 (m, 1H), 7.95–7.96 (m, 2H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3): δ 8.1, 31.6, 127.8, 128.4, 132.7, 136.8, 200.6; IR (neat): 2978, 2938, 1689, 1597, 1583, 1449, 1354, 1220, 952, 746, 690 cm^{-1} ; HRMS (EI): Calculated for $\text{C}_9\text{H}_{10}\text{O}$ (M) $^+$ 134.0732, found 134.0730.

A Typical Experimental Procedure for the Reductive Aldol Reaction of α -Tosyloxy Ketone Derivatives is as Follows (Table 2, Entry 1). To a solution of TiI_4 (166.6 mg, 0.30 mmol) in ClCH_2CN (1.0 mL) was added a solution of α -tosyloxypropiophenone (**1f**) (45.7 mg, 0.15 mmol) in ClCH_2CN (1.0 mL) at room temperature under an argon atmosphere. The mixture was stirred at room temperature for 2 h. To the resulting solution was added a solution of benzaldehyde (10.6 mg, 0.10 mmol) in chlorobenzene (1.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with saturated aqueous NaHCO_3 , and EtOAc and 10% aqueous NaHSO_3 were added successively. The mixture was filtered through a Celite pad, and extracted with EtOAc . The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by preparative silica gel TLC (hexane– $\text{EtOAc} = 4:1$ as an eluent) to give a mixture of diastereomers. The diastereomers were separated by preparative silica gel TLC (toluene– $\text{EtOAc} = 15:1$ as an eluent, developed twice) to give *syn*-**3a** (18.6 mg) and *anti*-**3a** (3.4 mg), respectively (92% yield, *syn:anti* = 85:15).

(2*S,3*S**)-3-Hydroxy-2-methyl-1,3-diphenylpropan-1-one (*syn*-**3a**):** Colorless oil; $^1\text{H NMR}$ (500 MHz, CDCl_3): δ 1.19 (d, $J = 7.3$ Hz, 3H), 3.66 (brs, 1H), 3.70 (dd, $J = 3.1, 7.3$ Hz, 1H), 5.23 (d, $J = 3.1$ Hz, 1H), 7.24–7.27 (m, 1H), 7.32–7.35 (m, 2H), 7.39–7.41 (m, 2H), 7.45–7.48 (m, 2H), 7.56–7.59 (m, 1H), 7.92–7.93 (m, 2H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3): δ 11.2, 47.0, 73.1, 126.0, 127.3, 128.2, 128.4, 128.7, 133.5, 135.6, 141.8, 205.7; IR (neat): 3460 (OH), 1677 ($\text{C}=\text{O}$) cm^{-1} ; HRMS (EI): Calculated for $\text{C}_{16}\text{H}_{16}\text{O}_2$ (M) $^+$ 240.1150, found 240.1151.

(2*R,3*S**)-3-Hydroxy-2-methyl-1,3-diphenylpropan-1-one (*anti*-**3a**):** Colorless oil; $^1\text{H NMR}$ (500 MHz, CDCl_3): δ 1.07 (d, $J = 7.3$ Hz, 3H), 2.96 (d, $J = 4.6$ Hz, 1H), 3.80–3.86 (m, 1H), 5.00 (dd, $J = 4.6, 7.9$ Hz, 1H), 7.28–7.31 (m, 1H), 7.35–7.38 (m, 2H), 7.41–7.43 (m, 2H), 7.45–7.49 (m, 2H), 7.56–7.59 (m, 1H), 7.97–7.98 (m, 2H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3): δ 15.7, 48.0, 76.8, 126.7, 127.9, 128.4, 128.5, 128.6, 133.3, 136.7, 142.2, 204.9; IR (neat): 3460 (OH), 1678 ($\text{C}=\text{O}$) cm^{-1} ; HRMS (EI): Calculated for $\text{C}_{16}\text{H}_{16}\text{O}_2$ (M) $^+$ 240.1150, found 240.1151.

Supporting Information

$^1\text{H NMR}$, $^{13}\text{C NMR}$, and IR spectra of **3b–3h** are provided. This material is available free of charge on the web at <http://www.csj.jp/journals/bcsj/>.

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