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

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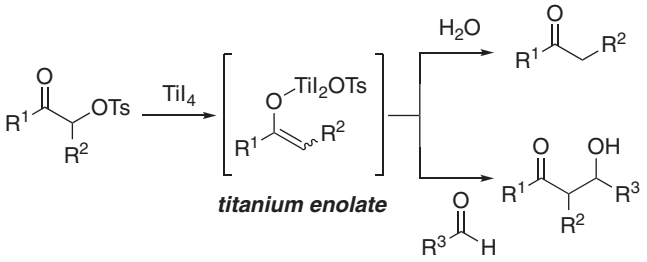
Titanium tetraiodide-promoted reductive enolate formation from α-tosyloxy ketone derivatives and subsequent aldol reaction of the resulting enolates with aldehydes gave β-hydroxy ketones.

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 chromium[3] 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).

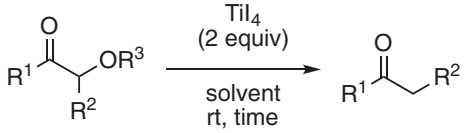
The effects of substituents in the oxygenated ketone derivatives and solvents were examined. Table 1 summarizes the results. When the reaction of α-benzyloxyacetophenone (**1a**) was carried out with TiI_4 in EtCN, debenzylation proceeded to give α-hydroxyacetophenone in 71% yield (Entry 1). We next 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-tosyloxypropiophenone (**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-tosyloxypropiophenone (**1f**), and benzaldehyde were investigated. When the reduction of α-tosyloxypropiophenone (**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 C_6H_5Cl, the desired



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



1a-f **2a-c**

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_6H_4	H	Ac	**1b**	EtCN	17	**2b** (74)
3	4-MeC_6H_4	H	Bz	**1c**	EtCN	17	**2b** (74)
4	4-MeC_6H_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.

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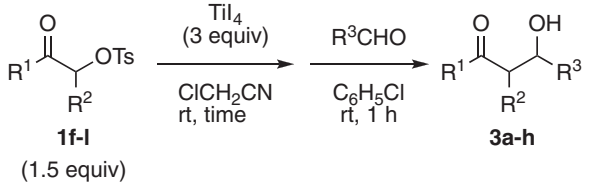
Table 2. Reductive Aldol Reaction of α-Tosyloxy Ketone Derivatives



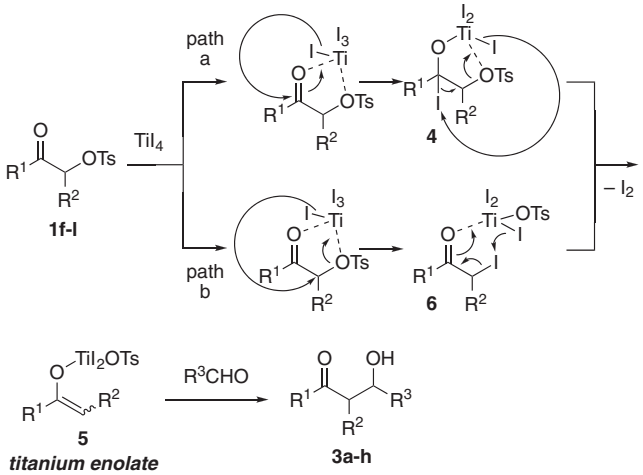
Entry	R^1	R^2	**1**	R^3	Time	**3**	Yield/% (*syn*:*anti*)[a]
1	Ph	Me	**1f**	Ph	2 h	**3a**	92 (85:15)
2	Ph	^{i}Pr	**1g**	Ph	1 h	**3b**	66 (32:68)[b]
3	Ph	Ph	**1h**	Ph	5 min	**3c**	36 (46:54)
4	^{t}Bu	Me	**1i**	Ph	2 h	**3d**	58 (96:4)[b]
5	Cy	Me	**1j**	Ph	2 h	**3e**	33 (51:49)[b]
6	2-furyl	Me	**1k**	Ph	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 ^{1}H NMR spectra. c) A mixture of ketone **1l** and benzaldehyde in $ClCH_2CN$ was added to a solution of TiI_4 in $ClCH_2CN$. 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 ^{i}Pr 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**) (R^1 = Ph, R^2 = 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 TiI_4 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 alternative method for the reduction of α-oxygenated ketone derivatives and their reaction.



Scheme 2. Possible mechanisms for the enolate formation.

Experimental

General. Infrared spectra were recorded on a JASCO FT/IR-460 Plus spectrometer. ^{1}H NMR spectra were recorded on a JEOL JNM α-500 spectrometer (500 MHz) with tetramethylsilane as an internal standard. ^{13}C 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 $CDCl_3$ (δ 77.0) as an internal reference. High-resolution mass spectra (EI) were recorded on a JEOL JMS-700D mass spectrometer. Propionitrile (EtCN) and chloroacetonitrile ($ClCH_2CN$) were distilled from P_2O_5 and then from CaH_2, and stored over molecular sieves 4A. Dichloromethane (CH_2Cl_2) was predried with P_2O_5, distilled from CaH_2, and stored over molecular sieves 4A. THF was distilled from benzophenone ketyl immediately before use. Toluene was predried with $CaCl_2$, 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 TiI_4 (166.6 mg, 0.30 mmol) in EtCN (1.0 mL) was added a solution α-tosyloxypropiophenone (**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 $NaHCO_3$, 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–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}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}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 $C_9H_{10}O$ $(M)^+$ 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–EtOAc = 4:1 as an eluent) to give a mixture of diastereomers. The diastereomers were separated by preparative silica gel TLC (toluene–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}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}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 (C=O) cm^{-1}; HRMS (EI): Calculated for $C_{16}H_{16}O_2$ $(M)^+$ 240.1150, found 240.1151.

(2*R,3*S**)-3-Hydroxy-2-methyl-1,3-diphenylpropan-1-one (*anti*-3a):** Colorless oil; ^{1}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}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 (C=O) cm^{-1}; HRMS (EI): Calculated for $C_{16}H_{16}O_2$ $(M)^+$ 240.1150, found 240.1151.

Supporting Information

^{1}H NMR, ^{13}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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