Reductive Aldol Reaction of α-Imino Esters Promoted by Titanium Tetraiodide: Selective Synthesis of α-Amino-β-hydroxyesters

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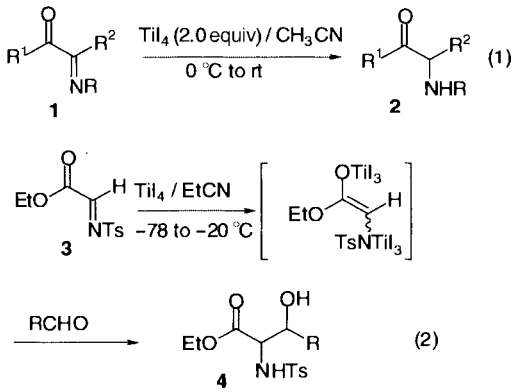
Under the influence of titanium tetraiodide reductive aldol reaction of *N*-tosylimines, derived from ethyl glyoxylate, with aldehydes proceeded to give α-amino-β-hydroxyesters in good yields.

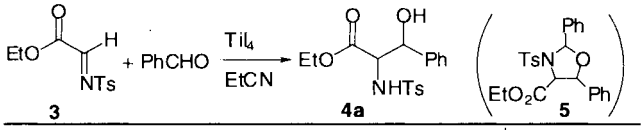
Amino alcohols have been received considerable attention as useful synthons in organic synthesis.[1] For the synthesis of such useful materials, the aldol reaction using enolates of α-amino carbonyl compounds is one of the most straightforward and powerful methods. Generally, generation of metal enolates from carbonyl compounds is carried out by abstraction of an acidic hydrogen α to carbonyl or by reductive metallation of α-halo ketones using organometallic compounds or low-valent metals.[2] It has already been reported that the Reformatsky reaction of α-halo ketones and aldehydes was promoted by low-valent metal species.[3] Formation of the tin enolates from *O*-stannyl ketyls was also reported under neutral free radical conditions.[4] Pinacol type cross-coupling of imines and aldehydes gave amino alcohols.[5] We have recently described that TiI_4 is an excellent reagent for pinacol coupling of aldehyde,[6] selective reductions of 1,2-diketones to α-hydroxy ketones[7] and of sulfoxides to sulfides,[8] and enolate formation from methoxyallene oxide.[9] Recent study has also revealed that TiI_4 is suitable for the selective reduction of imino ketones to amino ketones, where reductive formation of an enolate species may be involved (eq 1).[10] We have now found that TiI_4 affects the reductive aldol reaction of *N*-tosylimine **3,** derived from ethyl glyoxylate, with aldehydes to give α-amino-β-hydroxyesters **4** stereoselectively in good yields (eq 2).



Scheme 1.

First, optimum reaction conditions for reductive aldol reaction were investigated using the reaction of imino ester **3** and benzaldehyde, and the results are summarized in Table 1.

Table 1. Reductive aldol reaction of α-imino ester **3**: Comparison of reaction conditions[a]



3 **4a** **5**

Entry	TiI_4/equiv	Temp./°C	Yield of **4a** / %[b]	anti : syn[c]
1[d]	2.1	−78 – r.t.	64	55 : 44
2[e]	2.1	−45 – r.t.	65	84 : 16
3	2.1	−95 – r.t.	69	84 : 16
4	2.1	−78 – −20	73	81 : 19
5	2.1	−78 – −10	73	78 : 22
6	1.1	−78 – r.t.	24[f]	79 : 21
7	2.1	−78 – r.t.	66	83 : 17
8	3.0	−78 – r.t.	71	79 : 21

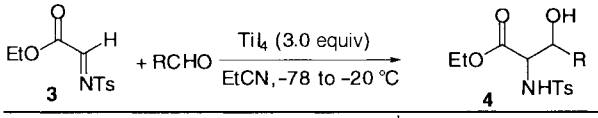
[a]Reaction was carried out according to the typical procedure.[11] [b]Isolated yield. [c]Determined by ^{1}H NMR (NOESY) on the corresponding acetonide.[12] [d]CH_2Cl_2 was used as a solvent. [e]CH_3CN was used as a solvent. [f]Compound **5** was obtained in 15% yield.

When the reaction was carried out in dichloromethane as a solvent, a very low diastereoselectivity was observed, whereas the use of propiononitrile and acetonitrile gave the desired product with good diastereoselectivity (entries 1–3). Better yields were obtained when the reaction was quenched at –20 to –10 °C (entries 4 and 5). Regarding the amount of titanium tetraiodide, while the use of one equivalent of titanium tetraiodide gave the adduct in low yield together with the cyclization product **5** as a byproduct, the use of an excess titanium tetraiodide gave better results (entries 6–8).

Under the optimum conditions, reductive aldol reaction with various aldehydes was carried out, and the results are summarized in Table 2. The reaction proceeded to give the adducts in good yields in most cases, and the case with 4-methoxybenzaldehyde gave the best yield of the aldol adduct (entry 2). This addition reaction is sensitive to the steric bulkiness of the aldehyde. When relatively bulky aldehydes were used, the reaction gave the adducts in low yields (entries 6 and 9). Although the product yield was not high, an excellent diastereoselectivity was observed in the case of 2,6-dichlorobenzaldehyde (entry 6).

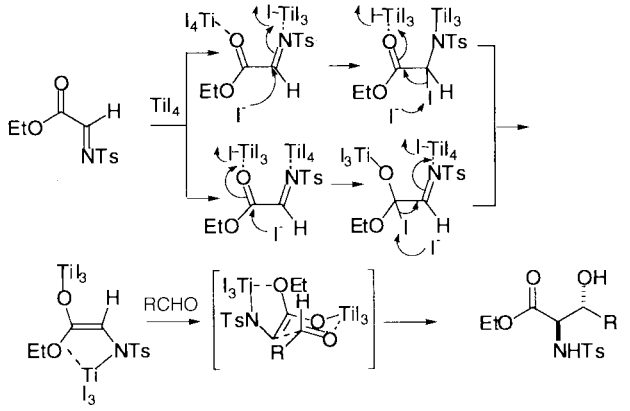
Although arguments on the stereochemical outcome need more experimental supports, the following scheme (Scheme 2) shows a possible reaction pathway. The present reaction appears to involve an initial attack of iodide anion at the imino or carbonyl carbon and the subsequent reaction with another iodide anion effects the formation of enolate species. The enolate thus generated reacts with aldehyde via a six membered cyclic transition state to give the *anti*-α-amino-β-hydroxyester selectively. Regarding the formation of *syn*-adducts in the

Table 2. Reductive aldol reaction of α-imino ester **3** with various aldehydes[a]



Entry	R	Yield/%[b]	anti : syn[c]
1	4-MeC_6H_4	74	77 : 23
2	4-$MeOC_6H_4$	87	74 : 26
3	4-ClC_6H_4	72	78 : 22
4	2-ClC_6H_4	63	59 : 41
5	1-Naphtyl	48	72 : 28
6	2,6-$Cl_2C_6H_3$	11	0 : 100
7	2,4-$(MeO)_2C_6H_3$	76	68 : 32
8	PhC≡C	46	33 : 67
9	*cyclo*-C_6H_{11}	32	23 : 77

[a]Reaction was carried out according to the typical procedure.[11] [b]Isolated yield. [c]Determined by ^{1}H NMR (NOESY) on the corresponding acetonides.[12]



Scheme 2.

cases with sterically hindered aldehydes, an acyclic transition state may explain the observed stereoselectivity.[13]

In conclusion, the reductive aldol reaction of *N*-tosyl imines, derived from ethyl glyoxylate, was promoted by TiI_4 and afforded α-amino-β-hydroxyesters selectively in good yields. Since titanium tetraiodide is commercially available and inexpensive, this procedure offers a convenient method for α-amino-β-hydroxyesters .

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References and Notes

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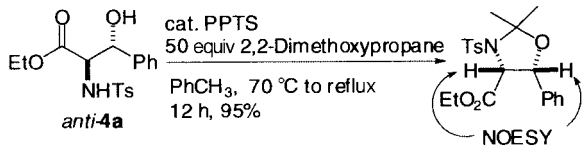
11 A typical procedure is as follows: Propiononitrile (1.0 mL) was added to TiI_4 (0.711 mmol) at ambient temperature under an argon atmosphere. After 10 min of stirring, to the solution of TiI_4 was added benzaldehyde (0.237 mmol) in propionitrile (1 mL) at –78 °C. After stirring for 30 min at –78 °C, ethyl 4-toluenesulfonyliminoacetate (0.237 mmol) was added at –78 °C, and the mixture was stirred at –78 °C to –20 °C for 4.0 h. The reaction was quenched with sat. aq $NaHCO_3$, 10% $NaHSO_3$, filtered through a Celite pad, and extracted with ethyl acetate (10 mL × 3). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification by flush column chromatography (*n*-hexane:ethyl acetate = 9:4 as an eluent) gave ethyl 3-hydroxy-3-phenyl-2-(4-toluenesulfonylamino)propionate (58.1 mg, 67%) as a colorless oil.

12 The relative stereochemistry of the product was determined using ^{1}H NMR (NOESY) after transforming it into the corresponding acetonide as in the following typical example, in which the *anti*-isomer showed correlation, whereas the *syn*-analogue did not:



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