A Catalytic Amount of Titanium Tetrahalide as Promoter for the Addition Reaction of Silyl Ketene Acetals to Imines

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In the presence of a catalytic amount of $TiBr_4$ or TiI_4, the reaction of silyl ketene acetals with imines smoothly proceeds to give the corresponding β-amino esters in high yield with high *anti*-selectivity.

The addition reaction of silyl ketene acetals with imines gave β-amino esters, which have been employed as precursors in the synthesis of β-lactams.[1] The reaction was usually promoted by the use of a stoichiometric amount of Lewis acid such as $TiCl_4$.[2] Recently the catalytic version of such addition reaction has been explored. Among the catalysts, TMSOTf,[3] $Bu_3P^+OP^+Bu_3(CF_3SO_3^-)_2$,[4] FeI_2,[5] $TrClO_4$,[5] $B(C_6F_6)_3$,[6] and $Yb(OTf)_3$[7] have been reported to be useful, although some of them are not readily available and/or require tedious experimental procedures. Titanium halides have been used frequently for a number of reactions,[8] and are commercially available. The efficiency as Lewis acid is influenced by the halogen atoms in the titanium halides.[9] We have been interested in the effect of halogen atoms in the titanium halides and already disclosed switchover of the diastereoselectivity induced by a simple selection of TiF_4 and $TiCl_4$ in the reaction of silyl ketene acetals with a chiral imine.[10] We would like to report that the addition reaction of silyl ketene acetals with imines was successfully catalyzed with $TiBr_4$ and TiI_4, in which the ability as catalyst was highly dependent on the halogen of the titanium halides.

The addition reaction in the presence of titanium halides was carried out in the following manner: to a solution of TiX_4 (0.020 mmol) and imine **1** (38.9 mg, 0.20 mmol) in CH_2Cl_2 (4 ml) was added dropwise a solution of silyl ketene acetal **2** (64 mg, 0.40 mmol) in CH_2Cl_2 (2 ml) at -78 °C, and the mixture was allowed to stand at -78 °C for 15 h. The mixture was quenched by adding aq. $NaHCO_3$. Usual workup gave an oil, which was purified on preparative TLC to give *anti*-β-amino ester **3**.[11]

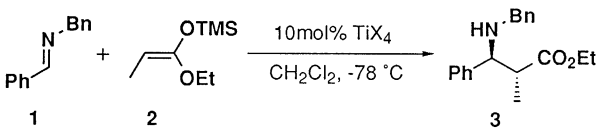


Table 1. Titanium halide (10 mol%) promoted addition reaction of silyl ketene acetal **2** with imine **1**

Entry	TiX_4	Yield / %[a]	*anti* : *syn*[b]
1	TiF_4	42	92 : 8
2	$TiCl_4$	53	93 : 7
3	$TiBr_4$	98	95 : 5
4	TiI_4	99	97 : 3

[a]Isolated yields. [b]The ratio was determined by 500MHz ^1H-NMR analysis.

Table 1 shows the results of the addition reaction of silyl ketene acetal **2** with *N*-benzylimine **1** promoted by 10 mol% of the titanium halides. By changing the halogen of the titanium halides from fluorine, chlorine, bromine, to iodine, the yield as well as selectivity was improved. The reaction of imine **1** in the presence of TiF_4 or $TiCl_4$ resulted in the turnover of 4~5 times. By employing $TiBr_4$ or TiI_4, the selectivity was improved and the turnover of the catalyst was much increased. In the presence of $TiBr_4$ the reaction smoothly proceeded to give β-amino ester **3** in 98% yield with an isomeric ratio of *anti* : *syn* = 95 : 5 (entry 3), whereas with TiI_4 the reaction gave β-amino ester **3** in 99% with *anti* : *syn* = 97 : 3 (entry 4). It is considered that the transfer of the active Lewis acid from the adduct to the imino nitrogen would be facilitated with $TiBr_4$ and TiI_4 which have relatively low Lewis acidity as compared with that of TiF_4 and $TiCl_4$, resulting in an efficient catalytic system.

Under the best conditions obtained by the use of TiI_4 catalyst, the reactions of various silyl ketene acetals and imines were carried out, and the results are shown in Table 2. Even in the presence of 1 mol% catalyst, the β-amino ester was obtained in good yield with high *anti*-preference, and in particular TiI_4 catalyst resulted in the turnover of over 90 times (entry 7). Both *E*- and *Z*-silyl ketene acetals gave *anti*-products as major diastereomers, since it was assumed that the reaction would proceed through an acyclic intermediate in an analogy to the aldol reaction (entries 9 & 10).[12] An aliphatic enolizable imine gave the adduct in moderate yield (entry 12). In contrast to *N*-

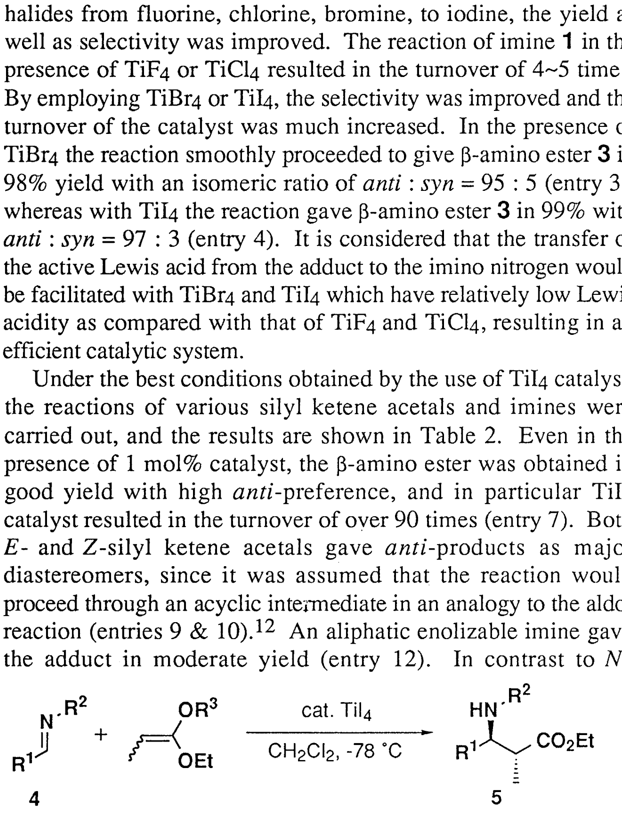


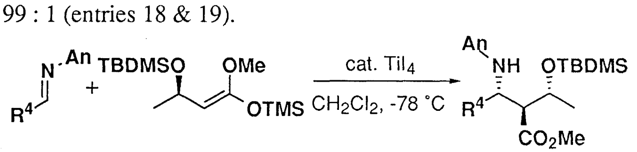
Table 2. Titanium iodide promoted addition reaction of silyl ketene acetals with imines **4**

Entry	Imine(R^1,R^2)	SKA(R^3)	TiI_4/mol%	Yield/%[a]	*anti* : *syn*[b]
5	Ph, Bn	TMS[f]	10	99	97 : 3
6	Ph, Bn	TMS	5	94	95 : 5
7	Ph, Bn	TMS	1	94	95 : 5
8	Ph, Bn	TMS	0.5	61	88 : 12
9	Ph, Bn	*E*-TBDMS[g]	10	54	91 : 9
10	Ph, Bn	*Z*-TBDMS[h]	10	65	87 : 13
11	Fr[c], Bn	TMS	10	78	77 : 26
12	Pr[d], Bn	TMS	10	77	60 : 40
13	Ph, An[e]	TMS	10	96	56 : 44
14	Ph, An	*E*-TBDMS	10	92	46 : 54
15	Ph, Ph	TMS	10	99	55 : 44

[a]Isolated yields. [b]The ratio was determined by 500MHz ^1H-NMR analysis. [c]Fr = Furyl group. [d]Pr = *n*-Propyl group. [e]An = Anisyl group. [f]*E* : *Z* = 92 : 8. [g]*E* : *Z* = 98 : 2. [h]*E* : *Z* = 13 : 87.

benzylimine the corresponding *N*-aryl imines showed no appreciable level of diastereoselectivity, in which product yields were always high even in the case with TBDMS acetal (entries 13, 14, & 15).

The chiral version of the present catalytic system was next investigated. Chiral silyl ketene acetal **7**[11] was synthesized from (*R*)-methyl 3-hydroxybutyrate, and was initially used in the reaction with achiral imine **4** (R^1 = Ph, R^2 = Bn) in the presence of TiI_4 catalyst. However, the product yield (41%) and the ratio of four possible isomers (1 : 5 : 72 : 22) were not satisfactory, and therefore the use of the anisyl derivative **6** was next investigated. The results are shown in Table 3. In the presence of 10 mol% catalyst, the reaction of chiral silyl ketene acetal **7** gave chiral β-amino ester **8**[12] in 94% yield with a ratio of *syn* : *anti* = 2 : 98 in which *anti*-adduct contained (2*S*,3*S*)- and (2*R*,3*R*)-isomers in a ratio of 98 : 2 (entry 16). By the use of furyl group in place of phenyl group, the selectivity was improved with a ratio of *syn* : *anti* = 1 : 99, (2*S*,3*S*) : (2*R*,3*R*) = 99 : 1 (entries 18 & 19).



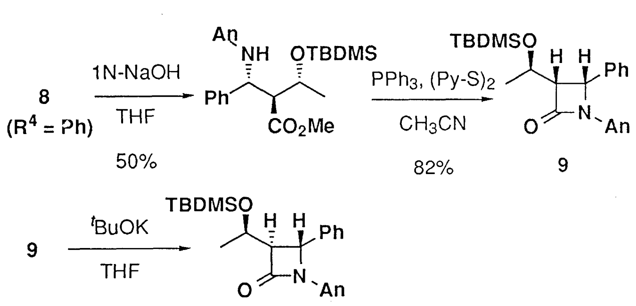
6 **7**(*E* : *Z* = 99 : 1) **8**

Table 3. Titanium iodide promoted addition reaction of chiral silyl ketene acetal **7** with achiral imines **6**

Entry	R^4	TiI_4/mol%	Yield/%[a]	*syn* : *anti* ((2*S*,3*S*) : (2*R*,3*R*))[b]
16	Ph	10	94	2 : 98 (98 : 2)
17	Ph	5	93	3 : 97 (99 : 1)
18	Fr[c]	10	96	1 : 99 (99 : 1)
19	Fr	5	85	1 : 99 (99 : 1)

[a]Isolated yields. [b]The ratio was determined by HPLC. [c]Fr = Furyl group.

Chiral β-amino ester **8** was converted into the corresponding chiral β-lactam **9**[13] by hydrolysis and cyclization. The relative stereochemistry at C_3 and C_4 of β-lactam **9** was determined to be *cis*-form by the vicinal coupling constant between C_3 and C_4 protons in ^{1}H-NMR spectrum (*J* = 5.49 Hz). The *cis*-β-lactam **9** thus obtained was isomerized into *trans*-β-lactam **10**, and the absolute stereochemistry of β-lactam **10** was determined to be (3*S*,3'*R*,4*S*)-form by comparison of the ^{1}H-NMR spectrum with that reported.[14] Thus, β-amino ester **8** obtained by the addition reaction was determined to be (2*S*,2'*R*,3*S*)-form.



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	H-3	H-3'	H-4	$J_{3,4}$(Hz)
10	3.17	4.32	4.88	2.4
lit. (3*S*,3'*R*,4*S*)	3.17	4.31	4.88	-
lit. (3*R*,3'*R*,4*S*)	3.06	4.37	5.17	-

In summary, β-amino esters were synthesized in good yields from imines and silyl ketene acetals in the presence of a catalytic amount of TiI_4, in which the effects of halogen of the titanium halides are noteworthy. The use of chiral silyl ketene acetal in the presence of TiI_4 gave chiral β-amino ester also in high yield with high selectivity. $TiBr_4$ and TiI_4 have potential as a mild Lewis acid catalyst.

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11 The stereochemistry of the products was determined by the vicinal coupling constant between C_2 and C_3 protons of the products by 500 MHz ^{1}H-NMR spectrum ($J_{anti} > J_{syn}$).[6]

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14 ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.08 (s, 3H), 0.11 (s, 3H), 0.91 (s, 9H), 1.20 (d, 3H, *J* = 6.72Hz), 2.91-2.98 (m, 1H), 3.39 (s, 3H), 3.67 (s, 3H), 4.31-4.36 (m, 1H), 4.71 (d, 1H, *J* = 7.94 Hz), 6.49 (d, 2H, *J* = 8.55 Hz), 6.66 (d, 2H, *J* = 8.55 Hz), 7.17-7.32 (m, 5H).

15 ^{1}H-NMR (500 MHz, $CDCl_3$) δ -0.50 (s, 3H), -0.20 (s, 3H), 0.74 (s, 9H), 1.34 (d, 3H, *J* = 6.72 Hz), 3.81 (dd, 1H, *J* = 5.49, 8.85 Hz), 3.73 (s, 3H), 3.96-4.01 (m, 1H), 5.15 (d, 2H, *J* = 5.49 Hz), 6.75 (d, 2H, *J* = 9.16 Hz), 7.18 (d, 2H, *J* = 9.16 Hz), 7.26-7.35 (m, 5H).

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