Highly Diastereoselective Addition Reaction of Ketene Silyl Acetals to Imines Catalyzed by Samarium(III) Iodide

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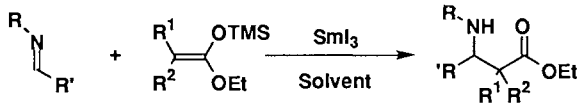
(Received April 2, 1999; CL-990248)

In the presence of a catalytic amount of a samarium(III) iodide, the addition reaction of ketene silyl acetal to imine afforded the corresponding β-aminoester with high *anti*-selectivity. The reaction of chiral imine under the same conditions gave β-aminoester with high diastereoselectivity.

β-Lactam antibiotics such as thienamycin and related carbapenems have attracted the attention of organic chemists as synthetic targets, because they possess broad range of high antibacterial activities.[1] The addition reaction of ketene silyl acetals to imine is one of the most convenient methods to form β-aminoesters, useful precursors of β-lactams. The reaction usually proceeds using a stoichiometric or catalytic amount of a Lewis acid such as trimethylsilyl triflate, phosphonium salts, FeI_2, trityl hexachloroantimonate, tris(pentafluorophenyl)boron, lanthanoide triflates, and TiI_4.[2] However, only a few examples have been reported to give the adducts in a highly diastereoselective manner. On the other hand, there is much current interest in the use of a lanthanoid catalyst as the Lewis acid because of its affinity for oxygen and activity as a Lewis acid. While many lanthanoid catalysts have been developed for the reaction of carbonyl compounds,[3] Kobayashi et al. reported the lanthanoid triflate-catalyzed reaction of imine in the presence of amine,[2e] which offers a limited example in an imino version. We have been interested in the activation of the imino functionality by a catalytic use of a Lewis acid and already disclosed the TiI_4-catalyzed reaction. Samarium(III) iodide has not been used as a Lewis acid, although samarium(II) iodide is a useful reducing agent.[4] Samarium(III) iodide is readily prepared *in situ* from samarium(II) iodide and iodine. We now wish to report a highly diastereoselective imino-aldol reaction using a catalytic amount of samarium(III) iodide.



1 : R = An, R' = Ph
2 : R = Bn, R' = Ph
3 : R = Bn, R' = *n*Pr
4 : R = Bn, R' = 2-Furyl
5 : R = Bn, R' = CH=CHPh

A typical procedure is as follows: To a propionitrile solution of iodine (3 mg, 0.012 mmol) was added a THF solution of samarium(II) iodide (0.024 mmol) at room temperature under an argon atmosphere to prepare samarium(III) iodide. To the resulting pale yellow solution was added a propionitrile solution of benzylidenebenzylamine (46.3 mg, 0.24 mmol) and 1-ethoxy-1-trimethylsiloxypropene (60.2 mg, 0.36 mmol) dropwise at -78 °C. The reaction mixture was allowed to warm to room temperature. After 15 h, to the reaction mixture was added brine, and the resulting mixture was extracted with ethyl acetate (15 ml x 3). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified on preparative TLC to give pure β-aminoester (99% yield, *anti* : *syn* = 93 : 7).[5]

Table 1. Addition reaction of ketene silyl acetal to achiral imine[a]

Entry	Imine	R^1, R^2	Solvent	Yield/%[b]	*anti* : *syn*[c]
1	**1**	Me, Me	THF	95	-
2	**2**	Me, Me	THF	62	-
3	**2**	Me, Me	EtCN	95	-
4	**3**	Me, Me	EtCN	53	-
5	**4**	Me, Me	EtCN	83	-
6	**1**	H, Me[d]	THF	90	67 : 33
7	**2**	H, Me[d]	EtCN	99	93 : 7
8	**5**	H, Me[d]	EtCN	39	>99 : 1

[a]The reaction was carried out in the presence of SmI_3 (10 mol%). [b]Isolated yield. [c]Determined by ^1H NMR (500 MHz). [d]*E* : *Z* = 91 : 9.

The results of the addition reaction of ketene silyl acetal to achiral imine **1-5** are summarized in Table 1. The addition reaction of 1-ethoxy-1-trimethylsiloxy-2-methylpropene to benzylidene-*p*-methoxyphenylamine in THF proceeded smoothly to give the corresponding β-aminoester in high yield (Entry 1). The yield of the reaction of benzylidenebenzylamine under the same reaction conditions was moderate (Entry 2). The use of propionitrile as a solvent instead of THF improved the chemical yield up to 95% yield (Entry 3). An aliphatic enolizable imine gave the product in moderate yield, while aromatic imines gave the corresponding β-aminoesters in high yields (entry 4 & 5). Diastereoselective addition reaction was investigated using 1-ethoxy-1-trimethylsiloxypropene (*E* : *Z* = 91 : 9). The addition reaction of 1-ethoxy-1-trimethylsiloxypropene with benzylidene-*p*-methoxyphenylamine afforded the corresponding *anti*-β-aminoester in high yield, although the selectivity was moderate (Entry 6). Use of $SmCl_3$ instead of SmI_3 as a catalyst decrease the yield of the amino ester,which may be due to the low solbility of the catalyst. The use of benzylidenebenzylamine gave the best result, in which the addition reaction proceeded to give the *anti*-β-aminoester in 99% yield with a ratio of *anti* : *syn* = 93 : 7. The best *anti*-selectivity was achieved using cinnamylidenbenzylamine as imine to give the *anti*-β-aminoester as the sole product.

The addition reaction of ketene silyl acetal to chiral imine was next investigated, and the results are summarized in Table 2. The reaction of chiral imine **6** possessing a 1,3-dioxolane ring derived from (2*S*,3*S*)-1,4-dimethoxymethyl-2,3-butanediol as a chiral auxiliary[6] with various ketene silyl acetals gave the chiral β-aminoester with high diastereoselectivity. The absolute configuration was established by its comversion to the known β-lactam and comparison of the ^1H NMR spectrum.[6] The reaction of 1-ethoxy-1-trimethoxyethylene in the presence of SmI_3 (10 mol%) in propionitrile at -78 °C to rt afforded the corresponding β-aminoester in 54% yield with moderate diastereoselectivity. The use of 1-ethoxy-1-trimethylsiloxy-2-methylpropene

enhanced both the chemical yield and diastereoselectivity. Moreover, the reaction of 1-ethoxy-1-trimethylsilyloxypropene with chiral imine **6** gave predominantly (2*S*,3*S*)- β-aminoester in 49% yield with a ratio of 3*S* (*syn*/*anti*): 3*R* = 93 (85/15) : 7. The moderate chemical yield would be due to the low nucleophilicity of the ketene silyl acetal (Entries 1 & 3), while 2,2-dimethyl derivative was obtained in high yield because of the high reactivity of 1-ethoxy-1-trimethylsiloxy-2-methylpropene (Entry 2).

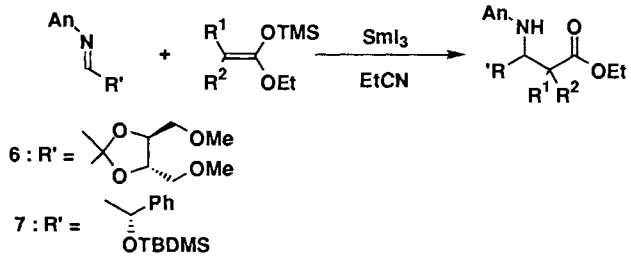
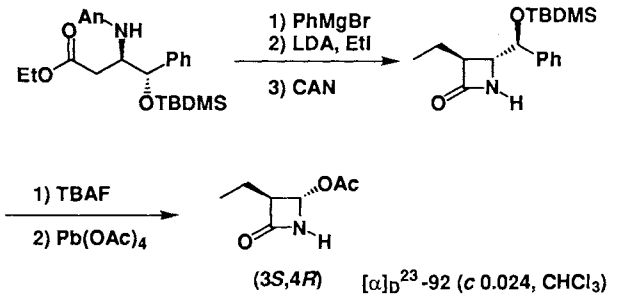


Table 2. Addition reaction of ketene silyl acetal to chiral imine[a]

Entry	Imine	R^1, R^2	Yield/%[b]	3*R* : 3*S* (*syn* : *anti*)[c]
1	**6**	H, H	54	16 : 84
2	**6**	Me, Me	98	4 : 96
3	**6**	H, Me[d]	49	7 : 93 (85 : 15)
4	**7**	H, H	38	>99 : 1
5	**7**	Me, Me	61	>99 : 1

[a]The reaction was carried out in the presence of SmI_3 (10 mol%). [b]Isolated yield. [c]Determined by HPLC (Hibar column, Merck). [d]*E* : *Z* = 91 : 9.

Diastereomerically pure β-aminoester was obtained using chiral imine **7** derived from (*S*)-mandelic acid. The addition reaction of 1-ethoxy-1-trimethylsiloxyethylene to chiral imine **7** in the presence of SmI_3 (10 mol%) in propionitrile gave the 3*S*-isomer as the sole product in 38% yield. Furthermore, an improved yield was obtained in the reaction of 1-ethoxy-1-trimethylsiloxy-2-methylpropene with chiral imine **7** to give the 3*R*-isomer in 61% yield.[7] The absolute configuration was determined to be 3*R* by its conversion to the known β-lactam and comparison of the optical rotation and ^{1}H NMR spectrum.[8] The stereochemical outcome could be explained by the Felkin-Anh transition state model.



In conclusion, we have demonstrated that the catalytic use of samarium triiodide in imino-aldol reaction was an efficient method to give β-aminoester with high *anti*-selectivity in the reaction of achiral imine, and high diastereoselectivity was obtained in the chiral version. Thus, the present method provides a useful entry into the preparation of β-aminoester.

Support of this research by the Ministry of Education, Science and Culture of the Japanese Government is gratfully appreciated.

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5 ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.90 (t, *J* = 6.9 Hz, 3H), 1.26 (t, *J* = 7.26 Hz, 3H), 3.51 (dd, *J* = 3.2, 29.0 Hz, 2H), 3.73 (d, *J* = 9.89 Hz, 1H), 4.18 (dq, *J* = 2.64, 7.25 Hz, 2H), 4.74 (br, 1H), 7.20-7.39 (m, 10H). IR (neat) 2975, 1730, 1458, 1260, 1180, 700 cm^{-1}.

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7 ^{1}H NMR ($CDCl_3$, 270 MHz) δ -0.50 (s, 3H), 0.0 (s, 3H), 0.86 (s, 9H), 1.16 (s, 3H), 1.17 (t, *J* = 7.26 Hz, 3H), 1.20 (s, 3H), 3.60 (s, 3H), 4.17 (br, 1H), 4.03 (q, *J* = 6.93 Hz, 2H), 4.42 (br, 1H), 4.66 (s, 1H), 6.30 (d, *J* = 8.91 Hz, 2H), 6.51 (d, *J* = 8.91 Hz, 2H), 7.00-7.09 (m, 5H). IR (neat) 3950, 1735, 1690, 1470, 1445, 1265, 1140, 700 cm^{-1}.

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