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A Convenient Method for Stereoselective Synthesis of β-Aminoesters. Iron(II) Iodide or Trityl Hexachloroantimonate as an Effective Catalyst in the Reaction of Ketene Silyl Acetals with Imines

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In the presence of a catalytic amount of iron(II) iodide or trityl hexachloroantimonate, ketene silyl acetals smoothly react with imines to afford the corresponding β-aminoesters in good yields with anti-selectivities.

The reaction of ketene silyl acetals with imines forming β-aminoesters, frequently employed as useful precursors in the synthesis of β-lactams, has been carried out by the use of a stoichiometric amount of Lewis acid such as $TiCl_4$1) or ZnI_2,2) or by the use of a catalytic amount of trimethylsilyl triflate (TMSOTf)3) or the phosphonium salt,4) However, few examples have been reported on the same reaction performed in a stereoselective manner by using a catalytic amount of promoter.

On the other hand, it is well known that metal iodides are employed as efficient catalysts in the reaction of ketene silyl acetals with various electrophiles. For examples, the above mentioned aldol type reaction between ketene silyl acetals and imines was carried out by the use of an equimolar amount of ZnI_2,2) and 1,4-addition of an enone with a ketene silyl acetal smoothly proceeded in the presence of a catalytic amount of HgI_2.5)

In the course of our investigations to search for an effective catalysts for a highly stereoselective β-aminoester synthesis from imines and ketene silyl acetals, various metal iodides were screened on the basis of the consideration that several metal iodides would have possibilities of working as highly active catalysts because of their comparatively low values of bond energies and affinities toward nitrogen-containing compounds. In addition, the use of various trityl salts, employed as good catalysts for a stereoselective aldol reaction,6) was studied.

First, the possibilities of using various metal iodides as catalysts were examined by taking the reaction of (E)-ketene silyl acetal of methyl propionate(**2**) and N-benzylideneaniline(**1**) as a model (Table 1, entries 1-6). Of various metal iodides screened, the use of a catalytic amount of iron(II) iodide (FeI_2) gave the corresponding β-aminoester in the best chemical yield (92%) with the highest anti-preference (anti/syn=82/18)(Table 1, entry 1). It was considered that there would be an alternative pathway of in situ generated iodotrimethylsilane (TMSI) catalyzed reaction, then the above mentioned reaction was tried by the use of a catalytic amount of TMSI to study the stereochemistry of the formed β-aminoester. The same reaction carried out in the presence of 10 mol% freshly distilled TMSI gave the β-aminoester with a slight syn-selectivity (anti/syn=45/55)(Table 1, entry 8) in distinction from the case of FeI_2 catalyzed reaction.

In addition, various trityl salts were screened by taking the above mentioned reaction as shown in Table 1 (entries 9-12). By using 5 mol% trityl hexachloroantimonate ($TrSbCl_6$), the corresponding β-aminoester was obtained in the best chemical yield (95%) with the highest anti-preference (anti/syn=92/8)(Table 1, entry 9). Thus, the FeI_2 or $TrSbCl_6$ mediated reaction of the ketene silyl acetal with the imine is performed in a high stereoselective manner.

Furthermore, various imines were treated with monosubstituted ketene silyl acetals in the presence of a catalytic amount of FeI_2 or $TrSbCl_6$ in order to study the stereochemistry of the present reaction. As shown in Table 2, $TrSbCl_6$ generally gave better results compared with FeI_2 in the reaction with N-phenyl imines, but in the case of the reaction of the N-phenyl imine 1 with the monosubstituted ketene silyl acetal of benzylester 3, the anti-preference arose by the use of FeI_2 catalyst (Table 2, entry 3). In the case of N-benzyl or N-diphenylmethyl imines, however, $TrSbCl_6$ gave lower yields in comparison with FeI_2 or seldom promoted the reactions.

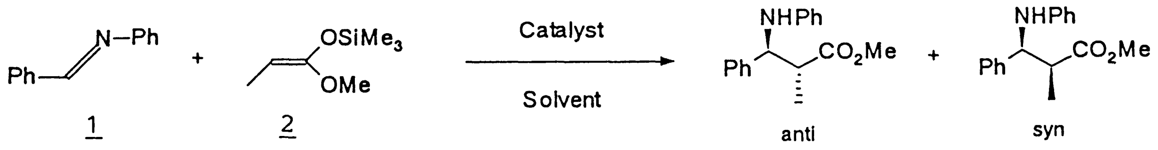


Table 1. Effect of Catalyst

Entry	Catalyst[a]	Solv.	Temp/°C	Time/h	Yield/%	Ratio of anti/syn[b]
1	FeI_2	CH_2Cl_2	-78	3	92	82/18
2	ZnI_2	Et_2O	-78	7	70	73/27
3	CdI_2	CH_2Cl_2	rt	24	68	73/27
4	HgI_2	Et_2O	rt	3	76	64/36
5	$TiCl_4$	CH_2Cl_2	rt	1	74	54/46
6	SnI_2	CH_2Cl_2	-78	24	68	49/51
7	TMSCl-$SnCl_2$	CH_2Cl_2	-78	3	73	46/54
8	TMSI	CH_2Cl_2	-78	3	92	45/55
9	$TrSbCl_6$	CH_2Cl_2	-78	0.25	95	92/ 8
10	$TrClO_4$	CH_2Cl_2	-78	1	86	84/16
11	TrCl-$SnCl_2$	CH_2Cl_2	-78	3	87	82/18
12	TrI	CH_2Cl_2	-78	3	78	45/55

Molar ratio of imine 1 : ketene silyl acetal 2 = 1.0 : 1.2.

a) Catalytic amount (10 mol%) except for entries 9 (5 mol%) and 5 (1 equiv.).

b) Determined by 500 MHz ^1H NMR.

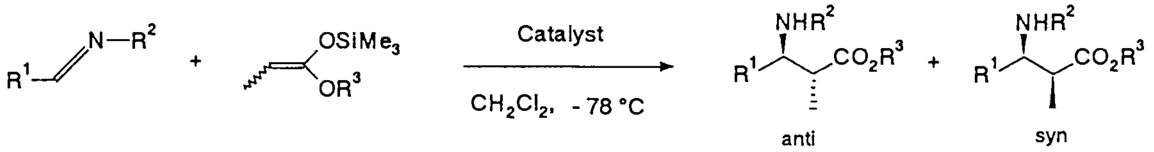
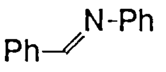
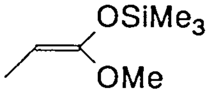
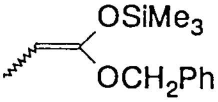
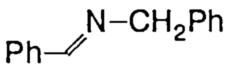
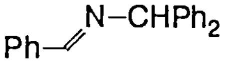
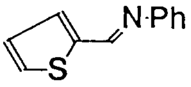
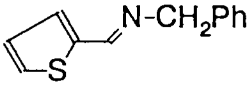
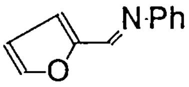
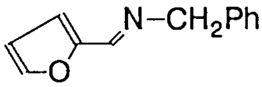
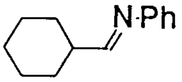


Table 2. Stereoselective Synthesis of β-Aminoesters[a]

Entry	Imine	Ketene silyl acetal	Catalyst[c] (10 mol%)	Yield/%	Ratio of anti/syn[e]
1	 1	 2 b) (E/Z = 100/0)	A	92	82/18
2			B[d]	95	92/ 8
3	1	 3 b) (E/Z = 84/16)	A	99	93/ 7
4		2	A	77	91/ 9
5			B	71	93/ 7
6		2	A	53	95/ 5
7		2	A	89	82/18
8			B[d]	84	98/ 2
9		2	A	65	93/ 7
10			B	47	94/ 6
11		2	A	92	81/19
12			B	91	67/33
13		2	A	73	74/26
14		2	A	68	75/25
15			B	50	73/27

Molar ratio of imine : ketene silyl acetal = 1.0 : 1.2.

[a] All products gave satisfactory ^1H NMR and IR spectral data.

[b] Determined by 60 MHz ^1H NMR.

[c] Catalyst A; FeI_2 : Catalyst B; $TrSbCl_6$.

[d] 5 mol%.

[e] Determined by 500 MHz ^1H NMR except for entries 14 and 15 (determined by isolated yield).

A typical procedure is described for the reaction of (E)-ketene silyl acetal of methyl propionate(**2**) with N-benzylideneaniline(**1**) (Table 1, entry 1): Under Ar, FeI_2 (12.3 mg, 0.04 mmol) in CH_2Cl_2 (2 ml) was stirred at room temperature for 30 min, then cooled to -78 °C. To the solution was successively added dropwise the imine **1** (72.5 mg, 0. 40 mmol) in CH_2Cl_2 (2 ml) and the ketene silyl acetal **2** (76.8 mg, 0.48 mmol) in CH_2Cl_2 (2 ml). After stirring for 3 h at -78 °C, the reaction mixture was quenched with aqueous solution of $NaHCO_3$. The organic materials were extracted with CH_2Cl_2 and the combined extracts were dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by preparative thin layer chromatography (SiO_2, hexane/ethyl acetate=5/1) to afford the corresponding β-aminoester in 92% yield (anti/syn=82/18). The stereochemistry was determined by 500 MHz ^1H NMR spectra ($CDCl_3$; $^3J_{2,3}$(Hz) anti 7.1, syn 4.8).

It is noted that β-aminoesters are synthesized in good yields with anti-selectivities under mild conditions from various imines and ketene silyl acetals by the use of a catalytic amount of FeI_2 or $TrSbCl_6$.

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