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HIGHLY DIASTEREOSELECTIVE ADDITION OF SILYL ENOLATES TO CHIRAL IMINES DERIVED FROM (S)-VALINE METHYL ESTER USING LANTHANIDE TRIFLATE.

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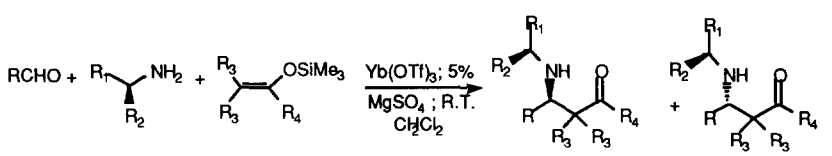
Abstract: One-pot highly diastereoselective synthesis of β–amino esters, precursors of β–amino acids and β–lactam antibiotics has been accomplished starting from an aldehyde, a chiral amine and a silyl enolate using $Yb(OTf)_3$ as a catalyst at room temperature. Excellent to good levels of diastereoselection have been achieved by the use of (S)-Valine methyl ester as chiral amine.

Addition of ester enolates to imines has been applied to the preparation of chiral β–amino ester derivatives, precursors of non proteinogenic β–amino acids[1] and β–lactam antibiotics[2].

One of the most useful methods for the synthesis of β-amino esters is the Lewis acid promoted reaction between silyl enolates and imines[3]. Recently, some methodologies that report the catalytic use of Lewis acid promoters such as trimethyl silyl triflate[4], phosphonium salts[5], FeI_2[6], trityl hexafluoroantimonate[6] , and $B(C_6F_5)_3$[7] were published. A great advance in catalytic Lewis acid aldol type reaction with imines was described by Kobayashi that reported the discovery of a highly efficient one-pot methodology for the preparation of β–amino esters with the use of lanthanide triflates[8].

Recently, we found[9] that high diastereoselection was achieved by the addition of allyl tributylstannane to a chiral imine derived from (S)-Valine methyl ester[10] in the presence of a catalytic amount of lanthanide triflates. We report here that chiral imines obtained through the *in-situ* procedure react with silyl enolates in a highly diastereoselective fashion *at room temperature* to afford chiral β–amino esters (Scheme **1**).

Scheme **1**



1 **2**

According our method catalytic amount of ytterbium triflate (5 mol.%) and anhydrous $MgSO_4$ were treated at room temperature with an aldehyde and a chiral amine, followed by addition of a silyl enolate[11]. We have chosen as chiral auxiliaries, the commercially available (S)-Phenylethylamine, (S)-2-Amino-3-phenyl-1-propanol, (S)-2-amino-2-phenylethanol, (S)-Valine methyl ester and (S)-Phenylglicyne methyl ester.

In Table 1 we report the results obtained with the chiral amines, benzaldehyde and the commmercially available 1-methoxy-1-trimethylsilyloxy-2-methyl-propene **3**[12] as model substrates.

Table 1. Diastereoselective Addition of The Silyl Enolate **3** to Chiral Imines Derived from Benzaldehyde.

Entry	R	R_1	R_2	R_3	R_4	Yield%[a]	d.r.[b]
1	Ph	Ph	Me	Me	OMe	85	65:35
2	"	CH_2OH	CH_2Ph	"	"	70[c]	75:25
3	"	CH_2OH	Ph	"	"	65[d]	68:32
4	"	COOMe	Ph	"	"	70	68:32
5	"	COOMe	*i*-Pr	"	"	62	92:8
6	"	"	"	"	"	70[e]	97:3

a) Isolated yield after flash chromatography. b) Diastereoisomeric ratio was evaluated by GC-MS analysis. The most abundant diastereoisomer was first eluted. c) The product was isolated as its O-silylated amino ester. d) 50% of lactonized product was isolated. The lactonized product showed the same diastereoisomeric ratio as the uncycled compound. e) Pure isolated imine was used.

The best results were achieved using (S)-Valine methyl ester as chiral amine while amino alcohols gave low diastereoisomeric excesses (entry 2 and 3). The efficiency of the (S)- Valine methyl ester as chiral auxiliary in this reaction was tested with aliphatic and aromatic aldehydes, and the results obtained are collected in Table **2.**

Table 2. Diastereoselective Synthesis of β-Amino Esters from Aldehydes, the Silyl Enolate **3** and (S)-Valine Methyl Ester.

Entry	R	R_1	R_2	R_3	R_4	Yield%[a]	**1** : **2**[b]
1	*i*-Pr	COOMe	*i*-Pr	Me	OMe	72	89:11
2	cyclohexyl	"	"	"	"	74	90:10
3	*n*-C_7H_{15}	"	"	"	"	63	71:29
4	*i*-Bu	"	"	"	"	76	68:32
5	2-Furyl	"	"	"	"	83	81:19
6	2-Py	"	"	"	"	72	93:7[c]
7	*p*-MeOPh	"	"	"	"	65	90:10
8	*m*-MeOPh	"	"	"	"	56	92:8

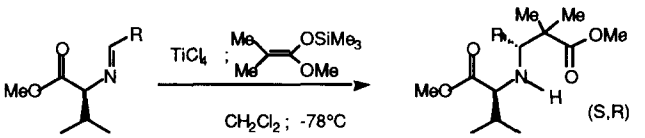
a) Isolated yield after chromatography. b) Diastereoisomeric ratio was evaluated by GC-MS and/or ^1H NMR spectroscopy. c) Pure diastereoisomer **1** was isolated after flash cromatography[13].

Working at room temperature,with branched aliphatic and aromatic aldehydes, we obtained good level of diastereoselection, while linear aliphatic aldehydes seemed not to give useful result with this methodology. We think that with aliphatic and aromatic aldehydes the formation of the E imine is favored under our reaction conditions.

The use of pure isolated E imine prepared from benzaldehyde and (S)-Valine methyl ester gives a diasteromeric ratio of 97:3 (entry 6, Table **1**). Similarly, the use of isolated E aliphatic imines does not change the diastereoselection obtained.

In the case of aliphatic aldehydes, the absolute configuration of the stereocenter formed in this reaction was established through the preparation of the corresponding β–amino ester using the method reported by Ojima[14]. (Scheme **2**).

Scheme **2**

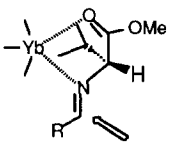


R=i-Bu,c-C_6H_{11},n-C_7H_{15}

The comparison of the retention time in GC analysis of the β–amino esters prepared using the two different procedures shows that the silyl enolate **3** preferentially attacks the Si face of the aliphatic imines derived from (S)-Valine methyl ester affording the β– amino ester with the (R) configuration of the new stereogenic center. We also propose that, in the case of aromatic and heterocyclic aldehydes,the attack occurs on the Si face of the imine derived from (S)-Valine methyl ester. We based our assumption on the observation that the most abundant diastereoisomer **1** always has a lower retention time in GC analysis.

To explain the result obtained in this reaction we suggest the model A as transition state in which the $Yb(OTf)_3$ is chelated by the nitrogen and the carbonyl group of the ester (Fig.**1**).

Fig. **1**



A

In order to show the generality of this reaction we have added the silyl enolate **4** derived from *tert*-butyl thio acetate to imines, prepared in situ from aromatic aldehydes, in the presence of catalytic amount of ytterbium triflate (5 mol.%).The excellent diastereoselections obtained by the use of (S)-Valine methyl ester as chiral amine are reported in Table **3**.

Table 3. Diastereoselective Addition of a Silyl Enolate **4** Derived from a t-Butyl Thio Acetate

Entry	R	R_1	R_2	R_3	R_4	Yield%[a]	d.r.[b,c]
1	Ph	Ph	Me	H	S-*t*-Bu	36	65:35
2	"	COOMe	*i*-Pr	"	"	60	96:4
3	2-Py	"	"	"	"	80	93:7[d]
4	*p*-MeOPh	"	"	"	"	40	91:9

a) Isolated yields after chromatography. b) Diastereoisomeric ratio was evaluated by ^1H NMR spectroscopy. c) The absolute configuration was not established. d) The most abundant diastereoisomer was isolated after flash cromatography[15].

In conclusion we have shown that high levels of diastereoselection have been achieved in the synthesis of the β-amino esters using chiral imines derived from (S)-Valine methyl ester in the presence of catalytic amount of

ytterbium triflate. Use of stereogenic and heterosubstituted silyl enolates as well as the employment of other amino acids or amino alcohols as chiral auxiliaries will be reported in the next future.

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References and Notes.

1. Juaristi, E;. Quintana, D.; Escalante, J. *Aldrichimica Acta* **1994**,*27*,3; and ref. therein.
2. Hart, D.J.; Ha, D.C. *Chem. Rev.* **1989**,*89*,1447. b) Brown, M.J. *Heterocycles* **1989**,*29*,2225. c) Van der Steen, F.K.; Van Koten, G.*Tetrahedron* **1991**,*47*,7503.
3. Gennari, C. In *Comprehensive Organic Synthesis;* Heathcock, Ed.; Pergamon, Oxford, U.K.,**1991**; Vol.2,p.629.
4. Guanti, G.; Narisano, E.; Banfi, L. *Tetrahedron Lett.* **1987**,*28*, 4331.
5. Mukaiyama,T.;Kashiwagi,K;. Matsui, S. *Chem. Lett.* **1989**,1397.
6. Mukaiyama,T.;Kashiwagi,K;. Matsui, S. *Chem. Lett.* **1989**,1397.
7. Ishihara, K.; Hanaki, N.; Funahashi, M.; Miyata,M.; Yamamoto, H. *Bull. Soc. Chim. JPN.* **1995**,*68*,1721.
8. Kobayashi,S.; Araki, M.; Yasuda,M. *Tetrahedron Lett.* **1995**,*36*,5773.
9. Bellucci, C.; Cozzi, P.G.; Umani-Ronchi, A. *Tetrahedron Lett.* **1995**,*36*,7289.
10. For the use of Valine methyl ester as chiral auxiliary see: a) Van Maenen,H;. Klejin, H.; JastrzebskiJ.T.B.H.; Verweij, J.; Kieboom, A.P.G.; Van Koten, G. *J. Org. Chem.* **1995**,*60*,4431. b) Waldemann, H.; Braun, M. *J. Org. Chem.* **1992**,*57*,4444. Waldemann,H. *Synlett* **1995**,133, and ref. therein.
11. A typical experimental procedure is the following: To a suspention of $Yb(OTf)_3$ (0.05mmol) and $MgSO_4$ (250mg) in CH_2Cl_2 (4mL) were added the aldehyde (1mmol.) and the (S)-Valine methyl ester (1mmol.) at room temperature. The mixture was stirred 0.5h and a silyl enolate was added to the same pot. The mixture was stirred for 24h then water was added and the product was extracted with CH_2Cl_2. The organic phase was collected, dried and evaporated to afford the crude product purified by flash cromatography.
12. For the diastereoselective addition of the silyl enolate **3** to chiral imines derived from carbohydrates see: Kunz,H.; Pfrengle,W. *Angew Chem., Int. Ed. Engl.* **1989**,*28*,1068.
13. Analytical data for the diastereoisomer **1** (R=2-Py; R_1=COOMe; R_2=*i*-Pr; R_3=Me; R_4=OMe): ^{1}H-NMR (300 MHz,$CDCl_3$): δ 8.51(dd,1H,J=4.88,0.94Hz); 7.63(dt,1H,J=7.48,1.7Hz); 7.42 (d,1H,J=7.48Hz); 7.18(dd,1H,J=7.48,4.88Hz); 3.86(s,1H); 3.70(s,3H); 3.67(s,3H); 3.42(d,1H,J=6.68Hz); 1.95-1.7(m,2H); 1.17(s,3H); 1.07(s,3H); 0.89(d,3H,J=6.68Hz); 0.82(d,3H,J=6.68Hz). $[\alpha]_D$= -86.7(c 0.93, $CHCl_3$)
14. Ojima, I.; Inaba, S. *Tetrahedron Lett.* **1980**,*21*,2080.
15. Analytical data for the most abundant diastereoisomer (R=2-Py; R_1=COOMe; R_2=*i*-Pr; R_3=H R_4=S-*t*-Bu): ^{1}H-NMR (300MHz,$CDCl_3$):δ8.54(dd,1H,J=4.02,0.87Hz);7.66(dt,1H,J=5.22,0.87Hz); 7.46(d,1H,J=6.3Hz); 7.17(dt,1H,J=5.22,=.87Hz); 4.2-4.05Hz(m,1H); 3.70(s,3H); 3-2.8(m,4H); 2-1.85(m,1H); 1.43(s,9H); 0.92(d,3H,J=6.78Hz); 0.89(d,3H,J=6.78Hz). $[\alpha]_D$= -37.9 (c 0.84, $CHCl_3$).

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