Diastereoselective Addition of Silyl Enol Ether to Chiral Imines and 1,3-Oxazolidines Using a Lewis Acid

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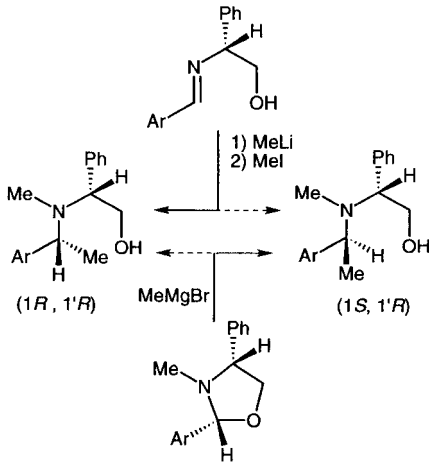
Abstract: The Lewis acid promoted reaction of silyl enol ether to chiral imines and 1,3-oxazolidines derived from (*R*)-phenylglycinol afforded with good diastereoselectivity the (*R*,*R*)-ß-amino ester derivatives from the imines, and the (*R*,*S*)-ß-amino ester derivatives from the 1,3-oxazolidines.

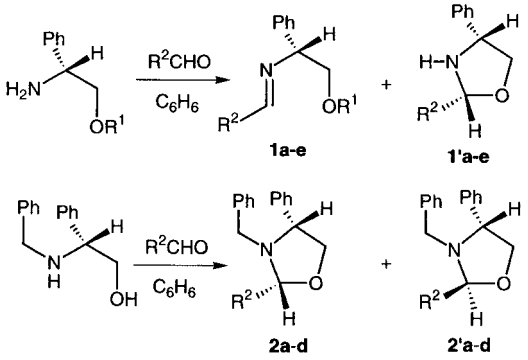
Chiral ß-amino acids are constituents of many classes of natural products, and important intermediates in the synthesis of ß-lactam derivatives.[1] Therefore, several approaches have been reported for their synthesis.[2] One of these approaches, the reaction of an imine with metal enolates or silyl enol ether under Lewis acid catalyzed conditions has been considered as a useful method for the synthesis of ß-amino acids.[3] Recently, we developed a synthetic method for the stereoselective preparation of both amine enantiomers starting from a single enantiomeric source using the diastereoselective addition of organometallic reagents to the chiral imines and 1,3-oxazolidines derived from (*R*)-phenylglycinol,[4] and we have already reported the application of such reactions to the asymmetric syntheses of naturally occurring alkaloids and chiral auxiliaries.[5]



Scheme 1

As a part of a program aimed at expanding the generality of this reaction, we envisaged that this reaction could be extended to the addition of silyl enol ether in place of organometallic reagents to give the ß-amino ester derivatives.

The desired starting material was readily prepared as follows. The condensation of the aldehyde (benzaldehyde, 2-furaldehyde, 2-thiophen carboxyaldehyde, acetaldehyde) with phenylglycinol, *O*-methylphenylglycinol[6] or *N*-benzylphenylglycinol[7] by heating in benzene with the azeotropic removal of water gave the chiral imines (**1a-e**) or 1,3-oxazolidines (**2a-d**) in quantitative yields. The ^{1}H-NMR spectrum in $CDCl_3$ of these products showed that **1a-c** were equilibrium mixtures of the imine form (**1a-e**) and 1,3-oxazolidine form (**1'a-e**), and also **2a-d** were inseparable thermodynamic mixtures, depending on the asymmetric center at the 2-position of the 1,3-oxazolidine ring.[8]



Scheme 2

Table 1. Condensation of (*R*)-Phenylglycinol, *O*-Methylphenylglycinol and (*R*)- *N*-Benzylphenylglycinol with Aldehydes

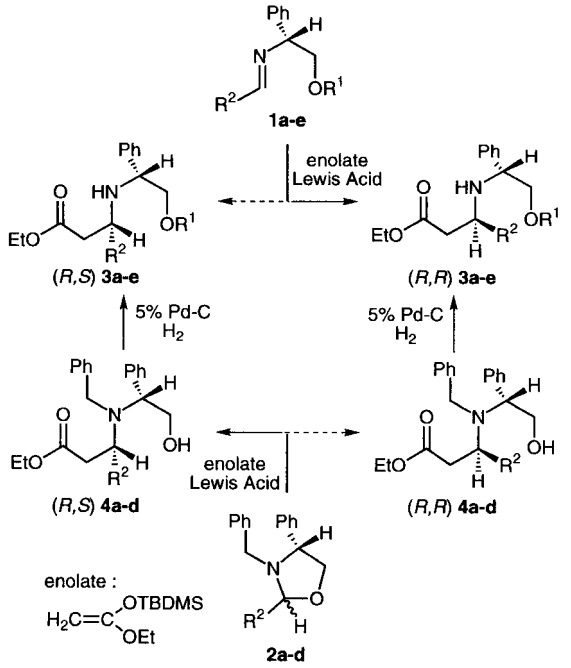
Compd.	R^1	R^2	Yield [a] (%)	Ratio [c] (1 : 1') or (2 : 2')
1a	H	Phenyl	94	83 : 7
1b	H	2-Furyl	85	94 : 6
1c	H	2-Thienyl	92	94 : 6
1d	CH_3	Phenyl	91	100 : 0
1e	CH_3	Methyl	98 [b]	100 : 0
2a	–	Phenyl	88	85 : 15
2b	–	2-Furyl	79	79 : 14
2c	–	2-Thienyl	76	86 : 14
2d	–	Methyl	90	88 : 12

a) Isolated yield. b) Crude yield.
c) Estimated by ^{1}H-NMR(270) spectrum

With the requisite compound available, we next carried out the reaction of a chiral imine (**1a**) with silyl enol ether[9] in the presence of various Lewis acids in CH_2Cl_2 at -78°C which resulted in pairs of diastereomeric adducts (**3a**). Although the reaction using $TiCl_4$, $SnCl_4$ or trimethylsilyl trifluoromethanesulfonate (TMSOTf) exhibited poor diastereoselectivities and chemical yields, the use of BF_3-OEt_2 as a Lewis acid obtained both good chemical yields and high diastereoselectivity (entry 4). In particular, for the reaction of chiral imines (**1b-c**) having aromatic heterocycles, essentially complete diastereoselectivity was obtained with good yields (entries 5 and 6), while in the case of an aliphatic imine (**1e**), poor results were obtained with this methodology (entry 8). Furthermore, it was found that chemical and optical yields in the addition of the silyl enol ether to the chiral imine (**1a**) having a hydroxyl group are satisfactory, but that the addition of the silyl enol ether to the chiral imine (**1d**) having a methyl ether group gives a surprisingly lower yield (entries 4 and 7). Therefore, it is believed that in these reactions, the hydroxyl group is an important factor in the selectivity process.

On the other hand, for the reaction of the oxazolidine (**2a**)[10] that used BF_3-OEt_2 or $SnCl_4$ as a Lewis acid, the proposed compound was not produced, but a complicated decomposition product was provided. In order to improve the lower yield, we examined several reaction conditions and finally found that the desired adducts (**4a**) could be obtained in high chemical and optical yields when TMSOTf was used.

The effect of the Lewis acid is shown in Table 2. It is of interest to note from Table 2 that the degree of diastereoselectivity of the addition is influenced by the kind of substituent at the 2-position on the 1,3-oxazolidine ring. Namely, the reactions of **1a-c**, which have an aromatic substituent, afford pairs of diastereomeric adducts (**4a-c**) with high diastereoselectivities (entries 12-14), but there is poor selectivity in the case of **2d** which has an aliphatic substituent (entry 15).



Scheme 3

Table 2. The Reaction of **1a-e** and **2a-d** with Silyl Enolate Using a Lewis Acid in CH_2Cl_2 at -78°C

Entry	Substrate	Lewis Acid (1.5equiv.)	Product	Yield [a] (%)	Ratio [b] (*RR* : *RS*)
1	**1a**	$TiCl_4$	**3a**	44	68 : 32
2	**1a**	$SnCl_4$	**3a**	20	89 : 11
3	**1a**	TMSOTf	**3a**	23	79 : 21
4	**1a**	BF_3-Et_2O	**3a**	78	97 : 3
5	**1b**	BF_3-Et_2O [c]	**3b**	84	99 : 1
6	**1c**	BF_3-Et_2O [c]	**3c**	85	99 : 1
7	**1d**	BF_3-Et_2O	**3d**	42	86 : 14
8	**1e**	BF_3-Et_2O	**3e**	trace	–
9	**2a**	BF_3-Et_2O	**4a**	trace	–
10	**2a**	$TiCl_4$	**4a**	52	9 : 91
11	**2a**	$SnCl_4$	**4a**	trace	–
12	**2a**	TMSOTf	**4a**	92	9 : 91
13	**2b**	TMSOTf [d]	**4b**	65	19 : 81
14	**2c**	TMSOTf [d]	**4c**	61	9 : 91
15	**2d**	TMSOTf	**4d**	94	34 : 66 [e]

a) Isolated yield, b) Estimated by ^{1}H-NMR (270MHz) spectrum,
c) Lewis Acid: 3 equiv., d) Reaction Temp. -50°C,
e) The configuration of the two diastereomers has not been determined

The absolute configurations of the newly formed chiral center in the adducts was determined as follows.

The ^{1}H and ^{13}C-NMR data for the major diastereoisomer (**3a**) isolated by column chromatography on silica gel were identical to those reported,[11] and optical rotation of our product ($[\alpha]_D^{21}$ -24.5 (*c*=2.0, $CHCl_3$)) corresponded well with the literature value ($[\alpha]_D^{25}$ -27.1 (*c*=1.0, $CHCl_3$)). [11] Furthermore, this compound was treated with MeI in the presence of KH to give the *O*-methyl product (**3d**) in quantitative yields, which was identified as the major product obtained from the reaction of the chiral imine (**1d**). Thus, the *R,R* configuration of major diastereoisomers (**3a** and **3d**) have been determined, and we think the other major diastereomers (**3b-c**) have the same configuration because these compounds are expected to be produced through a similar reaction mechanism. On the other hand, since the ß-amino esters (**4a-c**) derived from the 1,3-oxazolidines were unknown, the major diastereoisomers, also isolated by column chromatography, were submitted for reductive cleavage of the benzyl group with 5% Pd-C to afford the ß-amino esters (**3a-c**) in good yield, which were identical to the minor products obtained from the reaction of the imines (**1a-c**) with silyl enol ether based on ^{1}H-NMR spectral comparison.

Thus, the proposed method seems to be of wide interest in the synthesis of ß-amino acid derivatives since it can be applied to the selective preparation of both asymmetric carbon atoms from a single enantiomeric source. Further studies on the mechanistic and synthetic aspects of this stereoselective addition reaction are in progress.

References and Notes

1 a) 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.

2 a) *Enantioselective Synthesis of* β-*Amino Acids*; Juraristi, E., Ed.; Wiley-VCH Publishers: New York, 1996. b) Gennari, C. In *Comprehensive Organic Synthesis*, Heathcock, Ed.; Pergamon: Oxford, U.K., 1991; Vol. 2, p 629.

3 a) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry*, 1997, **8**, 1895. b) Guanti, G.; Narisano, E.; Banfi, L. *Tetrahedron Lett.*, 1987, **28**, 4331. c) Kobayashi, S.; Araki, M.; Yasuda, M. *Tetrahedron Lett.* 1995, **36**, 5773. d) Kobayashi, S.; Nagayama, S. *J. Org. Chem.*, 1997, **62**, 232. e) Loh, T.-P.; Wei, L.-L. *Tetrahedron Lett.*, 1998, **39**, 323.

4 Higashiyama, K.; Inoue, H.; Takahashi, H. *Tetrahedron Lett.*, 1992, **33**, 235.

5 a) Higashiyama, K.; Nakahata, K.; Takahashi, H. *Heterocycles*, 1992, **33**, 17. b) Higashiyama, K.; Nakahata, K.; Takahashi, H. *J. Chem. Soc., Perkin Trans. 1*, **1994**, 351. c) Higashiyama, K.; Inoue, H.; Takahashi, H. *Tetrahedron*, 1994, **50**, 1083. d) Higashiyama, K.; Inoue, H.; Ymauchu, T.;Takahashi, H. *J. Chem. Soc., Perkin Trans. 1*, **1995**, 111. e) Higashiyama, K.; Nakagawa, K.; Takahashi, H. *Heterocycles*, 1995, **41**, 2007.

6 Meyers, A. I.; Poindexter, G. S.; Brich, Z. *J. Org. Chem.*, 1978, **43**, 892.

7 Hunt, J. H.; McHale, D. *J. Chem. Soc.*, **1957**, 2073.

8 a) Agami, C.; Pizk, T. *Tetrahedron*, 1985, **41**, 537. b) Beckett, A. H.; Jones, G. R. *Tetrahedron*, 1977, **33**, 3313.

9 Colvin, E. W. In *Best Synthetic Methods, Silion in Organic Synthesis;* Katritsky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Academic Press: London, 1988; p 122.

10 Diastereoselective addition of silyl enol ether to oxazolidines has been reported. Berrien, J. F.; Billion, M. A.; Husson, H. P.; Royer, J. *J. Org. Chem.*, 1995, **60**, 2922.

11 a) Mokhallalati, M. K.; Wu, M-J.; Pridgen, L. N. *Tetrahedron Lett.*, 1993, **34**, 47. b) Mokhallalati, M. K.; Pridgen, L. N. *Synth. Commun.*, 1993, **23**, 2055.