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Stereoselective Synthesis of β-Amino Hydroxylamines

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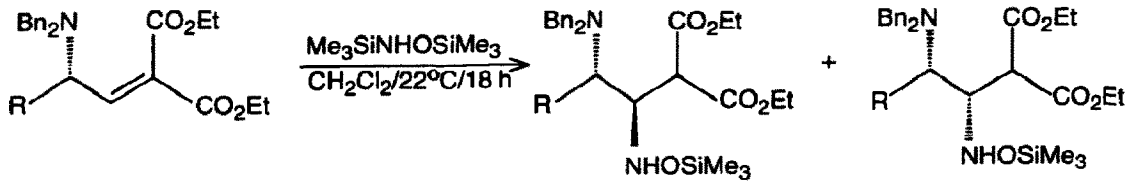
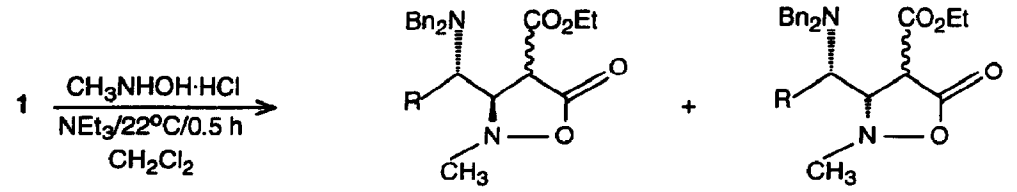
Abstract: *Chiral γ-N,N-dibenzylamino-substituted α,β-unsaturated carboxylic acid esters and dicarboxylic acid esters, prepared in enantiomerically pure form from L-amino acids, undergo diastereoselective Michael addition reactions with nitrogen nucleophiles of the type $Me_3SiNHOSiMe_3$ and CH_3NHOH; the products are novel β-amino hydroxylamine derivatives having two defined stereogenic centers.*

Chiral alkylidene-malonic acid esters of the type **1**, accessible in enantiomerically pure form from L-amino acids, have been shown to undergo stereoselective conjugate addition reactions with R_2CuLi and RMgX with formation of the corresponding anti-configurated γ-amino acids.[1,2] We now report that nitrogen nucleophiles, specifically hydroxylamines, also react stereoselectively in a 1,4-manner. Whereas primary amines such as $PhCH_2NH_2$ add to **1** mainly at the ester function with undesired formation of the amides,[2] the hydroxyl-amine $Me_3SiNHOSiMe_3$ undergoes smooth conjugate addition simply by stirring the components in CH_2Cl_2 at room temperature in the absence of catalysts:[3]



1	**2**		**3**
a) R = CH_3	95 (60%)	:	5
b) R = $PhCH_2$	94 (76%)	:	6
c) R = $(CH_3)_2CHCH_2$	91 (65%)	:	9

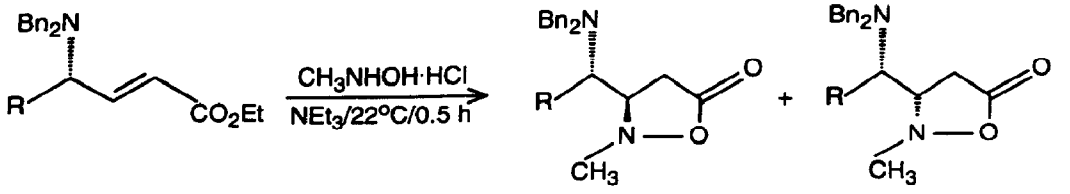
Upon performing a similar reaction with *N*-methyl-hydroxylamine, stereoselective addition was also observed. However, in this case concomitant ring-closure with formation of the novel isoxazolidinones **4 / 5** occurred.



	4		**5**
a)	83 (71%)	:	17
b)	92 (86%)	:	8
c)	90 (64%)	:	10

Of four possible diastereomers only two are observed. We ascribe these to **4/5** in which the additional stereogenic center bearing the ester group is formed in a completely stereoselective manner. Whereas the 1,2-stereochemical relation of the nitrogen functions is certain (see below), the configurational assignment of the additional stereogenic center is currently unclear. The vicinal coupling constants of the ring H-atoms amount to ~5.4 Hz, which may indicate a cis-relationship. Diastereoselectivity of CH_3NHOH-addition is thus slightly lower than in the reaction of the bulky reagent $Me_3SiNHOSiMe_3$.

The enantiomerically pure mono-esters **6** are known to react with R_2CuLi to afford preferentially the corresponding syn-configurated conjugate addition products,[1] although these substrates are less reactive and require Me_3SiCl as an additive in such cuprate reactions. Indeed, upon reacting **6** with $Me_3SiNHOSiMe_3$, an extremely sluggish reaction set in which is not synthetically useful. In contrast, CH_3NHOH reacted to form the isoxazolidones **7/8**. The reaction is slower and less stereoselective than the analogous process involving the more reactive Michael acceptors **1**. The reaction of **6a** is over after one day, whereas the bulky substrate **6c** requires 7 days (incomplete conversion). Nevertheless, substrates **6** make reversal of diastereofacial selectivity possible (compare **4** vs. **8**).



6 a) R = CH_3
b) R = $PhCH_2$
c) R = $(CH_3)_2CHCH_2$

	7		**8**
a)	10	:	90 (62%)
b)	27	:	73 (70%)
c)	36	:	64 (48%)

The configurational assignment of the major isomers **8** was made on the basis of an X-ray structural analysis of **8b** derived from L-phenylalanine (Fig. 1).[4] In the **4/5** series, **4b** was decarboxylated using NaCl/DMSO/H_2O, which afforded **7b**, obtained previously as the minor isomer in the reaction of **6b**. Although not checked in all cases, it is likely that the products are enantiomerically pure, especially in view of the fact that the starting materials **1** and **6** are pure (ee > 98%).[1] In order to gain definite proof, the adduct **2b** was subjected to hydrogenolysis using Pd/C, which led to the cleavage of the N-O bond. The corresponding primary amine was reacted with the R- and S-configurated "Mosher chlorides".[5] In each case the ^{1}H-, ^{13}C- and ^{19}F-NMR spectra showed a single set of signals, proving enantiomeric purity (ee > 98%).[2]

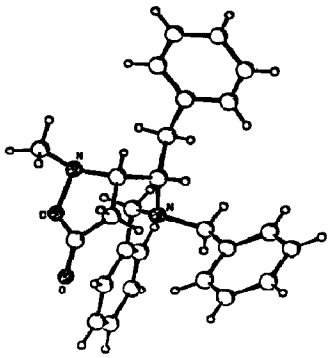
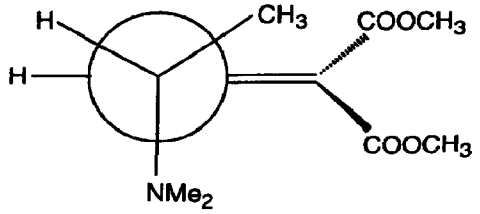


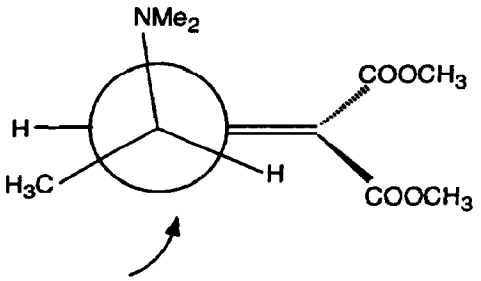
Fig. 1. X-ray crystal structure of **8b**

The origin of diastereofacial selectivity in the reactions of the diesters **1** is readily explained by invoking 1,3-allylic strain.[6] Using the *N,N*-dimethyl analog (of **1a**) , force field calculations (MM2)[7] were carried out.[2] Two conformers A and B were identified as energy minima, B being more stable by 12.5 kJ. This nicely corresponds to qualitative expectations based on 1,3-allylic strain. Nucleophilic attack from the si-side (cf. B) would afford the anti-adducts (as observed in the case of the reaction of esters **1**).



A

E_{rel} +12.5 kJ · mol^{-1}



B

0 kJ · mol^{-1}

Upon turning to the mono-esters **6**, the situation becomes more complicated.[1,8] Similar conformers were found,[2] but the difference in energy is almost negligible (1.4 kJ/mol). Thus, special effects in the transition state appear to be responsible, which need to be studied more closely by other theoretical methods.[9]

Acknowledgement

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References and Notes

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2. Röhrig, D. Dissertation, Universität Marburg, 1991.
3. Procedure: A diester **1**[1] (0.25 mmol) is dissolved in dry CH_2Cl_2 (1.0 ml) and treated with *N,O*-bis(trimethylsilyl)hydroxylamine (0.5 mmol) at 22°C under an atmosphere with N_2 for 18 h. The mixture is quenched with 2 ml of aqueous 2% HCl-solution and extracted twice with CH_2Cl_2. The combined org. phases are dried over $MgSO_4$. After removal of the solvent, the residue is chromatographed over SiO_2 (pet. ether/ether 4 : 1) to afford the anti-adducts **2** in the yields shown.
4. The X-ray data have been deposited at the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, England.
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7. Burkert, U.; Allinger, N. L. , "Molecular Mechanics", 2. ed., American Chemical Society, Washington, D. C. 1987; MacroModel (Version 1.1) according to W. C. Still was used in the calculations.
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