Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 6, pp. 1441-1450, 1995
Elsevier Science Ltd
Printed in Great Britain
0957-4166/95 $9.50+0.00

0957-4166(95)00177-8

Dramatic Solvents Effects on the Enantioselectivity of Chiral Oxazaborolidine Catalyzed Asymmetric 1,3-Dipolar Cycloadditions of Nitrones with Ketene Acetals†

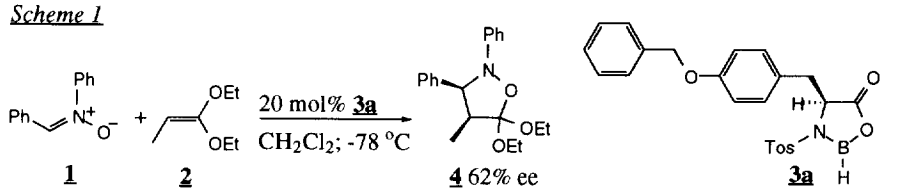
Jean-Paul G. Seerden, Marcel M.M. Kuypers, Hans W. Scheeren*

Department of Organic Chemistry , NSR Center for Molecular Structure, Design and Synthesis
University of Nijmegen, Toernooiveld, 6525 ED Nijmegen, The Netherlands

Abstract: *The enantioselectivity of the chiral oxazaborolidine catalyzed asymmetric 1,3-dipolar cycloaddition of nitrones with 1,1-dialkoxypropenes can be controlled by the α-side-chain substituent in the catalyst and the solvent. Remarkable reversal of enantioselectivity is achieved for catalysts having aryl substituents in the α-side-chain by addition of ligand-like solvents. Both enantiomers of a chiral β-amino ester have been prepared in two catalytic steps.*

The asymmetric 1,3-dipolar cycloaddition of nitrones is a key reaction in the synthesis of various biologically active compounds[1]. Moderate to good chiral induction has been achieved with chiral nitrones or chiral dipolarophiles[2]. Recently we reported the first example of catalytic asymmetric 1,3-dipolar cycloaddition of nitrones (*e.g.* C,N-diphenylnitrone **1**) with ketene O,O-dialkylacetals (*e.g.* 1,1-diethoxypropene **2**) catalyzed by 20 mol% chiral oxazaborolidines **3** derived from N-tosyl-*L*-α-amino acids and BH_3-THF (*Scheme 1*)[3a]. The chiral Lewis acid activates the nitrone by complexing the oxygen atom of the nitrone and lowering the LUMO energy. The electron-rich ketene O,O-dialkyl acetals are expected to give a LUMO(nitrone)-HOMO(alkene) controlled 1,3-dipolar cycloaddition[3]. The regio- and stereoselective formation of the *cis*-5,5-dialkoxy-isoxazolidine cycloadduct can be explained via the sterically less hindered transoid approach of the ketene acetal to the nitrone and formation of a dipolar intermediate[4]. The enantioselectivity was determined by the position of a phenyl group in the side-chain substituent of the chiral ligand analog to the chiral oxazaborolidine catalyzed Diels-Alder reaction of α,β-enals with simple dienes[5]. Considerable enhancement of enantioselectivity (up to 62% ee of (-)-**4**[3a]) was found with *L*-tyrosine(O-benzyl ether)-derived oxazaborolidine **3a**. Attractive donor-acceptor interactions[5,6] between the side-chain substituent of **3a** and the electron-poor C-phenyl part of the nitrone are believed to determine the enantioselectivity.

Scheme 1

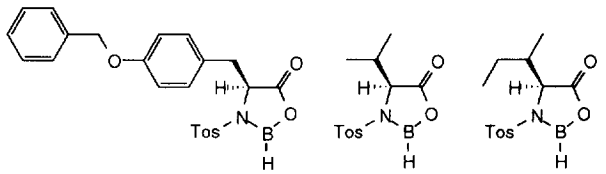


1 **2** **4** 62% ee **3a**

To gain further insight in the factors determining the enantioselectivity of the chiral oxazaborolidine catalyzed reaction of nitrone **1** with ketene acetal **2** we have studied the influence of the catalyst concentration, the α-side-chain substituent in the catalyst and the solvent[7]. In the standard procedure for 1,3-dipolar cycloaddition

3 equivalents of ketene acetal, 20 mol% chiral catalyst and a reaction temperature of -78 °C are used. It was found that the reaction can be performed with 1.5 equivalents of ketene acetal and 10 mol% chiral catalyst at -78 °C without any loss of reactivity, regio-, stereo- or enantioselectivity. As expected, the enantioselectivity decreases at higher temperatures from 62% ee at -78 °C to 32% ee at room temperature. Thus far, chiral ligands derived from α-amino acids containing phenyl groups were screened in order to find evidence that the position of a phenyl group could control enantioselectivity by attractive π-π donor-acceptor interactions. Further arguments on this phenomenon were provided by screening the influence on enantioselectivity of oxazaborolidines derived from amino acids lacking a donating aryl functionality in the side-chain substituent. Indeed, oxazaborolidines **3b** and **3c**, derived from BH_3-THF and resp. *L*-valine and *L*-isoleucine[8], gave substantially lower enantioselectivity than **3a** (Table 1).

Table 1. Reversal of Enantioselectivity in the Catalytic Asymmetric 1,3-Dipolar Cycloaddition of Nitrone **1** and Ketene Acetal **2** Catalyzed by Oxazaborolidines **3**[a].



3a **3b** **3c**

borane	e.e. **4** (%)	e.e. **4** (%)	e.e. **4** (%)
BH_3-THF	62 (-)	4 (-)	0
BH_3-SMe_2	48 (-)	70 (+)	73 (+)

[a]All reactions were run on a 1.0 mmol nitrone scale with 10 mol% oxazaborolidine **3** (*in situ* prepared from 1M BH_3-THF in THF or 1M BH_3-SMe_2 in CH_2Cl_2) and 1.5 eq. ketene acetal in 4 ml solvent at -78 °C.

Next, the influence of the starting borane-solution was studied. The *in situ* preparation of the chiral oxazaborolidine normally starts by adding an equimolar amount of commercially available BH_3-THF complex, as a 1M solution in THF, to the suspended N-tosyl-α-amino acid in dichloromethane. However, this preparation method introduces ca. 12 eq. THF in the reaction mixture. It has been reported by Helmchen that THF may influence association processes of the catalyst[7a]. To exclude donor solvents (like THF) from the reaction mixture the oxazaborolidines **3a**-**3c** were then also prepared from commercially available BH_3-SMe_2 as a 1M solution in CH_2Cl_2. The 1,3-dipolar cycloaddition of nitrone **1** with ketene acetal **2** catalyzed by **3a** now gave a slight decrease in enantioselectivity. Very surprisingly, a dramatical reversal of enantioselectivity was observed with the valine and isoleucine-derived catalysts **3b** and **3c** *in situ* prepared from 1 M BH_3-SMe_2 in CH_2Cl_2. The opposite enantiomer (+)-**4** was now obtained with resp. 70% and 73% ee (Table 1). These results demonstrate that the choice of a suitable solvent may be very important to obtain high enantioselectivities. From Table 1 it seems apparent that a donor solvent like THF does not interfere in the transition state of the 1,3-dipolar cycloaddition catalyzed by chiral oxazaborolidine **3a** in which the enantioselectivity is supposed to be determined by attractive π-π interactions. However, the presence of THF

has a dramatical effect on the enantioselectivity determined by steric hindrance in the transition state, as is expected for oxazaborolidines **3b** and **3c**. To study more systematically the influence of the solvent on the enantioselectivity of the 1,3-dipolar cycloaddition of nitrone **1** and ketene acetal **2** catalyzed by chiral oxazaborolidine **3a** several polar and polarizable solvents[9,10] were screened (Table 2). Special attention was paid to solvents with similar structures as the aromatic side-chain substituent in **3a** in order to study possible competitive effects on π-π interactions.

Table 2. Influence of Co-solvent on Enantioselectivity of the 1,3-Dipolar Cycloaddition of Nitrone **1** and Ketene Acetal **2** Catalyzed by Oxazaborolidine **3a** in CH_2Cl_2[a].

co-solvent[b]	% ee **4**	co-solvent[b]	% ee **4**
THF	62 (-)[3a,11]	EtCN	16 (+)
*t*BuOMe	26 (+)	$EtNO_2$	43 (+) 60 (+)[e]
*n*BuO*n*Bu	14 (+)	DMSO	6 (+)
PhOMe	4 (+)	sulfolan	15 (+)
PhOPh	58 (+) 79 (+)[c]	$PhNO_2$	33 (+)
$PhCH_2OCH_2Ph$	33 (+) 71 (+)[d]	PhI	8 (+)

[a]Reactions were run with 1.0 mmol nitrone and 10 mol% oxazaborolidine **3a** (*in situ* prepared from 1M BH_3-SMe_2 in CH_2Cl_2), 1.5 eq. ketene acetal in 4 ml solvent at -78 °C;[b] 0.1 ml (2.5 vol %) co-solvent; [c] 15 vol% co-solvent; [d] 7.5 vol% co-solvent; [e] 10 vol% co-solvent.

The results from Table 2 show that the presence of a co-solvent in the reaction mixture had dramatical effects on the enantioselectivity of the oxazaborolidine **3a** (from 1M BH_3-SMe_2 in CH_2Cl_2) catalyzed cycloaddition[12]. Except for THF, all co-solvents gave a reversal of enantioselectivity leading to the formation of (+)-**4**. This solvent effect is not simply related to increase or decrease of the polarity or polarizability of the solvent mixture. The striking structural similarities of diphenyl ether and dibenzyl ether with the side-chain substituent of **3a** suggest that most efficient solvation may occur with ligand-like solvents. Optimization of enantioselectivity was achieved by variation of the co-solvent concentration. For example, up to 79% ee of (+)-**4** was obtained in the presence of 15 vol% diphenyl ether as co-solvent additive. These results represent a conceptually new approach to the *stereoselective preparation of both enantiomers from a single chiral source by addition of ligand-mimicking donor-solvents*[13]. Unfortunately, the absolute configuration of the cycloadduct **4** or its derivatives is unknown so that transition state rationalizations are not possible.

In order to test the generality of these solvent effects we also studied the cycloaddition of C-phenyl-N-benzyl nitrone **5** with ketene acetal **6**. The application of N-benzyl nitrones[14] in 1,3-dipolar cycloaddition strategy towards natural products is particularly interesting because by simple debenzylation a primary amino

function can be introduced in the molecule. The chiral oxazaborolidine catalyzed 1,3-dipolar cycloaddition of N-benzyl nitrones with ketene acetals followed by a catalytic cleavage of N-O bond and debenzylation provides a very mild and convenient approach for asymmetric synthesis of β-amino esters in two catalytic steps[15]. The reaction of C-phenyl-N-benzyl nitrone **5** with ketene acetal **6** is strongly catalyzed by 20 mol% chiral oxazaborolidines **3** in dichloromethane at -78 °C to give regio- and stereoselectively the corresponding *cis*-2-benzyl-3-phenyl-4-methyl-5,5-dimethoxy-isoxazolidine **7** in a quantitative yield (*Scheme 2*, Table 3). The relative and absolute stereochemistry of **7** was established by converting the cycloadduct via one-step hydrogenolysis with hydrogen on $Pd(OH)_2$-C (Pearlman's catalyst)[16] to the known (*2R,3R*)-β-amino ester **8**[17]. The enantioselectivity was determined by chiral HPLC (Daicel Chiralcel OD column) of the enantiomers of β-amino ester **8** and or GC and ^1H- and ^{19}F-NMR analysis of the diastereomeric Mosher-amides[18].

Scheme 2

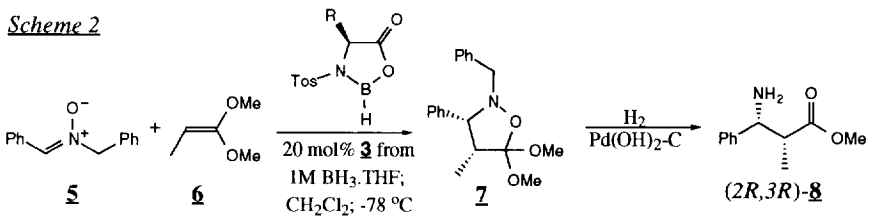


Table 3. Chiral Oxazaborolidine Catalyzed Asymmetric 1,3-Dipolar Cycloaddition of Nitrone **5** in CH_2Cl_2/THF

entry	substituent R in **3**	e.e. **8** (%)[a]
1	*i*-Bu	45
2	Ph	17
3	$PhCH_2$	11
4	$PhCH_2CH_2$	59
5	4-($PhCH_2O$)-$PhCH_2$	0
6	indolyl-CH_2	46

[a] In all cases the (*2R,3R*)- **8** enantiomer was formed in excess

Table 3 shows that highest enantioselectivity (59% ee) was obtained with a *L*-homophenylalanine-derived oxazaborolidine (entry 4). Remarkably, the tyrosine(O-benzyl ether)-derived oxazaborolidine **3a** (R= (4-(BzlO)-Ph)CH_2) which gives best enantioselectivity for reaction of nitrone **1** with ketene acetal **2** now suffers from any enantioselectivity (0% ee, entry 5). The position of the phenyl group in homophenylalanine is quite similar in tryptophane (R= indolyl-CH_2, entry 6) for which similar enantioselectivity was found. However, the isoleucine-derived oxazaborolidine (entry 1), lacking a phenyl group in the side-chain substituent, gave almost the same enantioselectivity. At the moment it is not clear if for the asymmetric 1,3-dipolar cycloaddition of nitrone **5** with ketene acetal **6** the enantioselectivity is controlled by the position of a phenyl group (via π-π attractive interactions) or by steric hindrance. Optimization procedures similar to nitrone **1** were followed. First, it was found that the use of 1.5 equivalents of ketene acetal **6** gave slow conversion of nitrone **5** in contrast to nitrone **1**. The use of 3 equivalents of the ketene acetal is necessary to obtain quantitative

conversion of the nitrone after 16-24 hours at -78 °C. Next, the influence of aliphatic side-chain substituents in oxazaborolidines, *in situ* prepared from BH_3-SMe_2, were studied in THF-free solution. The results in Table 4 show that the change of BH_3-THF to BH_3-SMe_2 has no effect on enantioselectivity arising from sterically demanding oxazaborolidines, e.g. **3b**, with aliphatic side-chains. However, considerable loss of *Re*-face selectivity was observed with oxazaborolidines **3d** (decrease from 59% ee to 11% ee; entry g) and **3e** (entry i) containing aromatic side-chain substituents. The latter gave even a small reversal of enantioselectivity with preferential formation of the opposite (*2S,3S*)-**8** enantiomer.

Table 4. Effect of Co-solvents on Enantioselectivity of 1,3-Dipolar Cycloaddition of Nitrone **5** with Ketene Acetal **6** Catalyzed by Chiral Oxazaborolidines **3**[a] Prepared from 1M BH_3-SMe_2

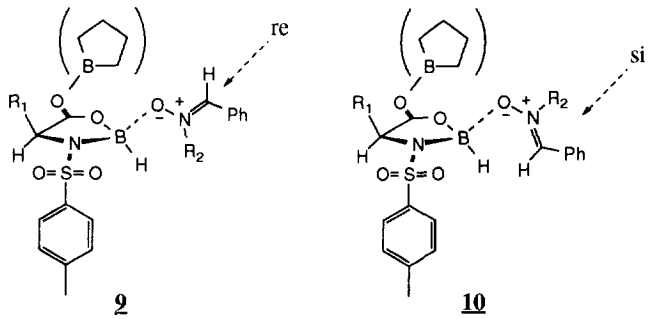
entry	catalyst	R	co-solvent[a]	vol%	e.e. (%) **8**
a	**3a**	4-($PhCH_2O$)-$PhCH_2$	-	-	8 (*2R,3R*)
b			$PhCH_3$	50	18 (*2S,3S*)
c			$PhCH_2OCH_2Ph$	2.5	34 (*2S,3S*)
d	**3b**	*i*-Pr	-	-	47 (*2R,3R*)
e			THF	100	21 (*2R,3R*)
f			$PhCH_3$	50	25 (*2R,3R*)
g	**3d**	$PhCH_2CH_2$	-	-	11 (*2R,3R*)
h			PhH	50	15 (*2S,3S*)
i	**3e**	Ph	-	-	10 (*2S,3S*)
j			$PhCH_2OCH_2Ph$	2.5	11 (*2S,3S*)
k			PhH	50	34 (*2S,3S*)
l			$PhCH_3$	50	40 (*2S,3S*)
m			$PhCH_3$	97.5	**74 (*2S,3S*)**
n			$PhCH_3$	100[b]	68 (*2S,3S*)

[a] dichloromethane used as standard solvent; catalyst preparation from BH_3-SMe_2 (1M in CH_2Cl_2);
[b] catalyst preparation from BH_3-SMe_2 (1M in toluene) and reaction in toluene as solvent.

The presence of ligand-like solvents (e.g. dibenzyl ether) gave a dramatical reversal of enantioselectivity in chiral oxazaborolidine **3a** catalyzed reaction of nitrone **1**. Likewise, the influence of co-solvents on the enantioselectivity of the asymmetric 1,3-dipolar cycloaddition of nitrone **7** catalyzed by various oxazaborolidines was studied. The results from Table 4 show that oxazaborolidines **3a**, **3d** and **3e** (with aromatic side-chain substituents) gave reversal of enantioselectivity to obtain (*2S,3S*)-**8** in the presence of aromatic solvents. For oxazaborolidine **3b** (with aliphatic side-chain substituent) *Re*-face enantioselectivity is retained in the presence of toluene. Optimization of the solvent effect up to 74% ee of (*2S,3S*)-**8** was achieved with the *L*-phenylglycine-derived oxazaborolidine **3e** (from 1M BH_3-SMe_2 in CH_2Cl_2) and toluene as solvent (entry m). No further increase of enantioselectivity was observed when preparing the catalyst **3e** from commercially available 1M BH_3-SMe_2 solution in toluene (entry n)[19].

The results outlined above demonstrate that the ability to control the enantioselectivity of these reactions with solvent seems rather general. The observed enantioface selectivities can be visualized by working models **9** and **10** which are based on the following assumptions: i) the nitrone (in its more reactive *E*-

configuration[20]) is complexed with the boron via the more basic oxygen atom; ii) all substituents of the oxazaborolidine ring are now positioned as far as possible from each other; iii) the conformers as depicted by **9** and **10**, obtained by rotation around the B-O, O-N and N-R_2 bonds of the *E*-nitrone part, are expected to be the more stable ones. Solvents effects can be explained by taking in account: i) solvent-dependent association of the catalyst via its carbonyl group; ii) solvent-dependent π-π-donor acceptor interactions of the aryl group in the side-chain substituent R_1 with the iminium part of the nitrone, and iii) solvent-dependency of conformer ratio **9**/**10**. Inspection of molecular models of the oxazaborolidine-nitrone complex clarifies that the flexible benzylic group (R_2= $PhCH_2$) is able to participate in shielding one of the two faces of the nitrone by rotation around the N-CH_2 bond. The complexicity of the system and the differences in enantioselectivities observed for a given catalyst between nitrone **1** and **5** do not allow us to speculate in more detail about the transition state.



9 **10**

In order to gain further insight in the chiral recognition mechanism we are currently investigating solvent effects in asymmetric 1,3-dipolar cycloadditions of rigid nitrones with a fixed geometry and the application of polymer-supported chiral oxazaborolidine catalysts in this reaction.

EXPERIMENTAL SECTION

When necessary, solvents and reagents were dried prior to use. Dichloromethane was dried and distilled on CaH_2 and tetrahydrofuran was distilled from benzophenone ketyl. All solvents were stored over 4Å molecular sieves. Diphenyl ether (solid) was melted before use. All reactions were carried out under dry nitrogen or argon atmosphere. ^{1}H-NMR spectra and ^{13}C-NMR were recorded on a Bruker AM-100 (100 MHz, FT) or a Bruker AM-400 (400 MHz, FT) spectrometer with TMS as internal standard. Gas chromatography was performed on a Hewlett-Packard 5710A GC-instrument equipped with a capillary HP cross-linked methyl silicone (25 m x 0.31 mm) column type PAS 017. Melting points were measured with a Reichert Thermopan microscope and are uncorrected. Optical rotation was measured with a Perkin-Elmer 241 polarimeter at the sodium D line. Enantioselectivities were determined with chiral HPLC analysis using Daicel CHIRALCEL OD and CHIRALPAK AD columns with *n*-hexane/2-propanol mixtures as eluens on a LKB HPLC apparatus (2150 pump, 2252 controller, 2138 UV-detector). Nitrones **1** and **5**[1h,14], ketene acetals **2** and **6**[21] and N-tosyl α-amino acids[8] were prepared according to literature procedures.

Chiral oxazaborolidine catalyzed 1,3-dipolar cycloaddition of nitrones with ketene acetals (General

procedure)

The chiral oxazaborolidines (0.2 mmol) were prepared *in situ* from N-tosyl-*L*-α-amino acids[8] at room temperature under inert nitrogen atmosphere by addition of equimolar amounts of BH_3-THF (1M solution in THF) or BH_3-SMe_2 (1M solution in CH_2Cl_2 or 1M solution in toluene) in dry solvent (total volume 4.0 ml)[3a]. Nitrone (1.0 mmol) was added at room temperature, the mixture cooled to -78 °C and the ketene acetal (1.5-3 eq.) was added. After 5-24 hours the nitrone was completely converted and the reaction mixture was quenched with saturated aqueous bicarbonate, extracted with dichloromethane and diethyl ether, dried with sodium sulphate and concentrated under vacuum. The crude 5,5-dialkoxyisoxazolidine was isolated in high yield (80-99%). Samples for chiral HPLC analysis were prepared on a small scale (ca. 10 mg) by further purification by flash chromatography on silica gel or alumina using ether:*n*-hexane (1:1-4) as eluens (containing 1% Et_3N) followed by concentration under vacuum.

2,3-diphenyl-4-methyl-5,5-diethoxy-isoxazolidine 4[16]

m.p. 93 °C; 400 MHz ^{1}H NMR δ(ppm) 0.78 3H, d, J = 7.2 Hz, 4-CH_3; 0.90 3H, t, J = 7.1 Hz, CH_3; 1.29 3H, t, J = 7.1 Hz, CH_3; 2.84 1H, quintet, J = 7.1 Hz and J = 6.9 Hz, H-4; 3.54-3.74 4H, m, 2x O-CH_2; 4.99 1H, d, J = 6.9 Hz, H-3; 6.87 3H, m, ArH; 7.16 2H, m, ArH; 7.31 3H, m, ArH; 7.41 2H, m, ArH. ^{13}C NMR δ(ppm) 11.1 (4-CH_3), 14.6 (CH_3), 15.0 (CH_3), 46.0 (C-4), 57.3 (CH_2), 59.5 (CH_2), 72.3 (C-3), 114.7, 120.9 (C-5), 121.0, 127.3, 127.4, 128.3, 128.5, 138.5 (C_{ipso}), 151.5 (C_{ipso}). HRMS (rel. int.) m/e : 328 (M^{+1}, 7), 327 (M^+, 34), 282 (-OEt, 37), 226 (12), 219 (95), 208 (10), 180 (51), 145 (56), 135 (38), 130 (100). Peak Match: M_{calc} = 327.1834, M_{found} = 327.18337 ±0.00096. $C_{20}H_{25}NO_3$ Calc. C 73.37, H 7.70, N 4.28 Found : C 73.36, H 7.70, N 4.34 . A sample of (-)-**4** with 62% enantiomeric purity gave optical rotation $[\alpha]_D^{25}$ = -57 (c=0.5 in $CHCl_3$). The enantioselectivity was determined by chiral HPLC on a Daicel CHIRALPAK AD column, UV 254 nm, flow rate 1.0 ml/min., eluens *n*-hexane/2-PrOH = 99/1, 10.10 min. (minor isomer) and 11.47 (major isomer). Until now the absolute configuration of (+)- or (-)-**4** is unknown.

5,5-dimethoxy-4-methyl-3-phenyl-N-benzyl isoxazolidine 7

oil; 400 MHz ^{1}H NMR δ (ppm) 0.78 3H, $J_{4CH3,H3}$=7.29 Hz, 4-CH_3; 2.73 1H, dq, $J_{H4,4CH3}$=7.18 Hz, $J_{H4,H3}$=6.90 Hz, H-4; 3.28 3H, s, 5-OCH_3; 3.36 3H, s, 5-OCH_3; 3.88 1H, d, J_{gem}=14.4 Hz, H-6a; 4.02 1H, d, J_{gem}=14.4 Hz, H-6b; 4.45 1H, d, $J_{H3,H4}$=6.9 Hz, H-3; 7.31 10H, m, H-arom. ^{13}C NMR δ(ppm) 10.8 (4-CH_3), 46.0 (C-4), 49.5 (5-OCH_3'), 50.5 (5-OCH_3), 61.9 (Ph$\underline{C}H_2$), 73.3 (C-3), 121.0 (C-5), 127.0 (C-Ar), 127.2 (C-Ar), 127.5 (C-Ar), 127.9 (C-Ar), 128.1 (C-Ar), 128.2 (C-Ar), 128.3 (C-Ar), 128.6 (C-Ar), 129.0 (C-Ar), 129.3 (C-Ar), 137.0 (C_{ipso}), 137.8 (C_{ipso}). HRMS (rel. int.) m/e : 314 (M^++1, 2), 313 (M^+, 10), 282 (-OCH_3, 2), 267 (-CH_3, 2), 226 (2), 213 (6), 212 (40), 194 (5), 191 (16), 149 (16), 121 (25), 102 (51), 91 (100). Peak Match: M_{calc} = 313.1678, M_{found} = 313.1672 ± 0.0009. Although the isoxazolidine **7** is not stable on silica gel and its purification by chromatography on silica gel gives a low-yielding oil, the hydrogenolysis of the crude isoxazolidine **7** gives the corresponding β-amino ester **8** in high yields (*vide infra*).

methyl (2R,3R)-3-amino-2-methyl-3-phenylpropionate 8[17]

To a solution of the crude isoxazolidine **7** (313 mg, 1 mmol) in methanol-water-acetic acid (20:2:1, 10 ml) was added $Pd(OH)_2$-C (Pearlman's catalyst[16], 250 mg) and the resultant black suspension stirred under a hydrogen balloon for 5 hours. The reaction mixture was then filtered through a plug of Celite, washing with

methanol and the filtrate concentrated to give a white residue. The residue was dissolved in sat. aq. $NaHCO_3$ which was subsequently extracted with dichloromethane. The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to afford the free β-amino ester (*2R,3R*)-**8** (175 mg, 90% yield). Samples for chiral HPLC analysis were prepared by further purification by flash chromatography on silica gel using methanol:ether (30:1) as eluens on a small scale (ca. 10 mg) followed by concentration under vacuum. Absolute configuration of (*2R,3R*)-**8** was established by a negative optical rotation. The enantiomer (*2S,3S*)-**8** was reported to give positive rotation $[\alpha]_D^{25}$ = +15.8 (c 1.00, $CHCl_3$)[17]. 400 MHz ^1H NMR δ (ppm) 1.16 3H, d, J = 7.1 Hz, 2-CH_3; 1.68 2H, br s, NH_2; 2.76 1H, dq, J = 5.9 and 7.1 Hz, H-2; 3.58 3H, s, OCH_3; 4.29 1H, d, J = 5.9 Hz, H-3; 7.24 1H, m, *para*-ArH; 7.26-7.32 4H, m, ArH. ^{13}C NMR δ (ppm) 11.9 (2-CH_3), 47.2 (C-2), 51.5 (OCH_3), 57.3 (C-3), 126.5, 127.2, 128.3 (Ar-C), 143.6 (C_{ipso}), 175.4 (C=O). HRMS (rel. int.) m/e : 193 (M^+, 0.3), 178 (-CH_3, 7), 177 (55), 158 (2), 145 (3), 132 (4), 122 (8), 121 (100), 105 (10). Peak Match: $C_{11}H_{15}NO_2$ M_{calc} = 193.1103, M_{found} = 193.11021 ± 0.00097. Enantioselectivity was determined by HPLC on Daicel chiral HPLC column type CHIRALCEL OD, UV 226 nm, eluens: *n*-hexane/2-PrOH = 99/1, flow rate 1.0 ml/min., (*2R,3R*)-**8** : 22.2 min. ; (*2S,3S*)-**8** : 36.0 min. The enantioselectivity was also determined by NMR-analysis of the derivatized Mosher-amides **11** and **12**. The β-amino ester (*2S,3S*)-**8** (HPLC 57% ee) was dissolved in dichloromethane and (*R*)-Mosher acid chloride was added[18]. After stirring at room temperature for 2 hours the crude mixture was separated with flash chromatography on a silica gel to afford the pure diastereomeric Mosher amide **11** and **12** as a 0.64: 2.36 mixture. oil; 400 MHz ^1H NMR δ (ppm) 1.11 0.64H, d, J = 7.1 Hz, 2-CH_3 (**11**); 1.17 2.36H, d, J = 7.1 Hz, 2-CH_3 (**12**); 3.02 1H, m, H-2; 3.38 0.64H, s, OMe; 3.47 2.36H, s, OMe; 3.56 0.64H, s, OMe; 3.60 2.36H, s, OMe; 5.32 1H, m, H-3; 7.13 1H, m, NH; 7.23-7.43 10H, m, ArH. ^{13}C NMR δ (ppm) 12.8, 2-Me(**11**), 13.1 2-Me, (**12**), 44.4 C-2, (**11**), 44.5 C-2, (**12**), 51.9 (OMe), 55.0 and 55.1 (OMe), 77.2, 122.3, 125.1, 126.7, 126.9, 127.5, 127.6, 127.8, 128.4, 128.5, 129.4, 129.8, 132.4, 138.6 (Ar-C), 165.5 (C=O), 173.9 (C=O). ^{19}F NMR δ (ppm) 11.00 s, CF_3 and 11.04 s, CF_3 (**11**). HRMS (rel. int.) m/e : 410 (M^{+1}, 0.3), 378 (-OMe, 2), 322 (10), 220 (20), 189 (32), 177 (55), 145 (3), 132 (3), 121 (100). Peak Match: $C_{21}H_{22}NO_4F_3$ M_{calc} = 409.1500, M_{found} = 409.1501 ± 0.001.

REFERENCES AND NOTES

† Partially presented at IKCOC-6, november 7-11, 1994, Kyoto, Japan, abstracts OP-33 and PP-092.

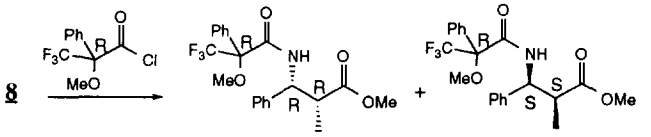
1. a) Tufariello, J.J. In *1,3-Dipolar Cycloadditions Chemistry*, Padwa, A., Ed.; Wiley, New York, **1984**, vol. 2, pp. 83-168; b) Confalone, P.N.; Huie, E.M. *Org. React.* **1988**, *36*, 1-173; c) Balasubramanian, N. *Org. Prep. Proc. Int.* **1985**, 25; d) Black, D.S.; Crozier, R.F.; Davis, V.C. *Synthesis*, **1975**, 205-221; e) Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Gazz. Chim. Ital.* **1989**, *119*, 253-269; f) Mulzer, J. *Nachr. Chem. Tech. Lab.* **1984**, *32*, 882-887; g) Torssell, K.B.G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*, VCH Weinheim, **1988**, pp. 1-47, 75-89, 129-327; h) Döpp, D.; Döpp, H. in "Houben-Weyl- Methoden der Organischen Chemie", vol E14b, Klamann, D.; Hagemann, H., Eds.; Georg Thieme Verlag: Stuttgart, **1990**; i) Grünanger, P.; Vita-Finzi, P. in '*The Chemistry of Heterocyclic Compounds*', Taylor, E.C., Ed., Vol. 49, part 1, Chapter 3 'Isoxazolidines', John Wiley & Sons, New York, **1991**, pp. 649-777.
2. a) Murahashi, S.-I.; Imada, Y.; Kohno, M.; Kawakami, T. *Synlett*, **1993**, 395-396 (ref. 2 and 3 cited therein); b) Mukai, C.; Kim, I.J.; Cho, W.J.; Kido, M.; Hanaoka, M. *J. Chem. Soc. Perkin Trans. 1* **1993**,

2495-2503; c) Murahashi, S.-i.; Sun, J.; Tsuda, T. *Tetrahedron Lett.* **1993**, *34*, 2645-2648; d) Goti, A.; Cicchi, S.; Brandi, A.; Pietrusiewitz, K.M. *Tetrahedron : Asymmetry* **1991**, *2*, 1371-1378; e) Takahashi, T.; Fujii, A.; Sugita, J.; Hagi, T.; Kitano, K.; Arai, Y.; Koizumi, T.; Shiro, M. *Tetrahedron : Asymmetry* **1991**, *2*, 1379-1390; f) Brandi, A.; Cicchi, S.; Goti, A.; Koprowski, M.; Pietrusiewicz, K.M. *J. Org. Chem.* **1994**, *59*, 1315-1318; g) Wovkulich, P.M.; Baggiolini, E.G.; Hennessy, B.M.; Uskokovic, M.R. *Heterocycles* **1993**, *35*, 791-797; h) Tamura, O.; Yamaguchi, T.; Noe, K.; Sakamoto, M. *Tetrahedron Lett.* **1993**, *34*, 4009-4010; i) Tamura, O.; Yamaguchi, T.; Okabe, T.; Sakamoto, M. *Synlett.* **1994**, 620-622; j) Konosu, T.; Oida, S. *Chem. Pharm. Bull.* **1993**, *41*, 1012-1018; k) Keller, E.; de Lange, B.; Rispens, M.T.; Feringa, B.L. *Tetrahedron* **1993**, *49*, 8899-8910; Rispens, M.T.; Keller, E.; de Lange, B.; Zijlstra, R.W.J.; Feringa, B.L. *Tetrahedron: Asymmetry* **1994**, *5*, 607-624; l) Gravestock, M.B.; Knight, D.W.; Lovell, J.S.; Thornton, S.R. *J. Chem. Soc. Perkin Trans. I* **1994**, 1661-1663; m) Saito, S.; Ishikawa, T.; Moriwake, T. *J. Org. Chem.* **1994**, *59*, 4375-4377; n) Naito, T.; Ikai, M.; Shirakawa, M.; Fujimoto, K.; Ninomiya, I.; Kiguchi, T. *J. Chem. Soc. Perkin Trans. I* **1994**, 773-775; o) Aurich, H.G.; Quintero, J.-L. R. *Tetrahedron* **1994**, *50*, 3929-3942; p) Oppolzer, W.; Deerberg, J.; Tamura, O. *Helv. Chim. Acta* **1994**, *77*, 554-560.

3. a) Seerden, J.-P.G.; Scholte op Reimer, A.W.A.; Scheeren, J.W. *Tetrahedron Lett.* **1994**, *35*, 4419-4422, the absolute configuration of cycloadduct **4** is arbitrarily chosen. For other non-catalytic examples of see: b) Scarpati, R.; Sica, D.; Santacroce, C. *Gazz. Chim. Ital.* **1966**, *96*, 375-386; c) Huisgen, R.; Grashey, R.; Seidl, H.; Hauck, H. *Chem. Ber.* **1968**, *101*, 2559-2563; d) Keirs, D.; Moffat, D.; Overton, K.; Tomanek, R. *J. Chem. Soc. Perkin Trans. I* **1991**, 1041-1051; e) Díaz-Ortiz, A.; Díez-Barra, E.; de la Hoz, A.; Prieto, P.; Moreno, A. *J. Chem. Soc. Perkin Trans I* **1994**, 3595-3598.
4. The alternative concerted reaction mechanism via an *endo*-approach of the ketene acetal would be accompanied by unfavoured steric interactions between the 2-methyl substituent of the ketene acetal and the C-phenyl group of the nitrone.
5. Seerden, J.-P.G.; Scheeren, J.W. *Tetrahedron Lett.* **1993**, *34*, 2669-2672.
6. For examples of attractive donor-acceptor interactions in catalytic asymmetric Diels-Alder reactions: Corey, E.J.; Roper, T.D.; Ishihara, K.; Sarakinos, G. *Tetrahedron Lett.* **1993**,*34*, 8399; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 1561; Hawkins, J.M.; Loren, S.; Nambu, M. *J. Am. Chem. Soc.* **1994**, *116*, 1657. Review : Sawamura, M.; Ito, Y. *Chem. Rev.* **1992**, *92*, 857-871.
7. a) other important variables in the system are the mode of preparation, age, and enantiomeric purity of the catalyst: Sartor, D.; Saffrich, J.; Helmchen, G.; Richards, C.J.; Lambert, H. *Tetrahedron: Asymmetry* **1991**, *2*, 639-642; b) for discussions about association processes of oxazaborolidines, see: Brown, J.B.; Lloyd-Jones, G.C.; Layzell, T.P. *Tetrahedron : Asymmetry* **1993**, *4*, 2151-2154; Nevalainen, V. *Tetrahedron:Asymmetry* **1991**, *2*, 827-842.
8. a) Houben-Weyl, *'Methoden der Organischen Chemie'*, Band 15/1, *Synthese von Peptiden* I, 4^{e}Auflage, Georg Thieme Verlag, Stuttgart, **1974**, pp. 223-233; b) Berry, M.B.; Craig, D. *Synlett*, **1992**, 41-44.
9. a) Carlson, R.; Lundstedt, T.; Albano, C. *Acta Chem. Scand. B*, **1985**, *39*, 79-91; b) Reichardt, C. *Angew. Chem.* **1979**, *91*, 119-131.
10. Reichardt, C., "Solvents and Solvent Effects in Organic Chemistry", 2nd ed., **1990**, VCH, Weinheim.
11. Only 2% ee was obtained when the **3a**-catalyzed reaction was performed in THF as solvent.
12. For examples of solvent-dependent enantioselectivity in chiral Lewis acid catalyzed asymmetric Diels-Alder and aldol reactions, see : Corey, E.J.; Loh, T.-P. *Tetrahedron Lett.* **1993**, *34*, 3979-3982; Corey, E.J.; Guzman-Perez, A.; Loh, T.-P. *J. Am. Chem. Soc.* **1994**, *116*, 3611-3612; Ishihara, K.; Gao, Q.;

Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 6917-6919; Kobayashi, S.; Fujishita, Y.; Mukaiyama, T. *Chem Lett.* **1990**, 1455-1458; Kobayashi, S.; Uchiro, H.; Shiina, I.; Mukaiyama, T. *Tetrahedron* **1993**, *49*, 1761-1772. In other reactions: Hiroi, K.; Arinaga, Y.; Ogino, T. *Chem. Lett.* **1992**, 2329; Froelich, O.; Bonin, M.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron: Asymmetry* **1993**, *4*, 2335-2338; Soai, K.; Suzuki, T.; Shono, T. *J. Chem. Soc., Chem. Commun.* **1994**, 317-318; Hansen, T.V.; Waagen, V.; Partali, V.; Anthonsen, H.W.; Anthonsen, T. *Tetrahedron: Asymmetry* **1995**, *6*, 499-504; Aune, M.; Gogoll, A.; Matsson, O. *J. Org. Chem* **1995**, *60*, 1356-1364; see also ref. 10, pp. 244-260.

13. a) for examples of reverse enantiofacial selectivities depending on solvent, see: Ando, K.; Takemasa, Y.; Tomioka, K.; Koga, K. *Tetrahedron* **1993**, *49*, 1579; b) Kobayashi, S.; Ishitani, H. *J. Am. Chem. Soc.* **1994**, *116*, 4083-4084; Kobayashi, S.; Ishitani, H.; Hachiya, I.; Araki, M. *Tetrahedron* **1994**, *50*, 11623-11636; c) the role of nitroethane is more difficult to understand. Strong solvation of the nitrone may hinder the usual attack of the ketene acetal. Attack on the rear side may be faster than desolvation.
14. a) Murahashi, S.-I.; Shiota, T.; Imada, Y. *Org. Synth. Vol. 70*, **1992**, 265-271; b) Goti, A.; De Sarlo, F.; Romani, M. *Tetrahedron Lett.* **1994**, *35*, 6571-6574; c) Dondoni, A.; Franco, S.; Junquera, F.; Merchán, F.; Merino, P.; Tejero, T. *Synth. Commun.* **1994**, *24*, 2537-2550.
15. Reviews on stereoselective preparation of β-amino acids: Cole, D.C. *Tetrahedron* **1994**, *50*, 9517-9582; Juaristi, E.; Quintana, D.; Escalante, J. *Aldrichimica Acta* **1994**, *27*, 3.
16. Pearlman, W.M. *Tetrahedron Lett.* **1967**, *17*, 1663.
17. a) Davies, S.G.; Garrido, N.M.; Ichihara, O.; Walters, I.A.S. *J. Chem. Soc., Chem. Commun.* **1993**, 1153-1155; b) Davies, S.G.; Ichihara, O.; Walters, I.A.S. *J. Chem. Soc., Perkin Trans. I* **1994**, 1141-1147.
18. Preparation of Mosher-amides according to: Dale, J.A.; Mosher, H.S. *J. Am. Chem. Soc.* **1973**, *95*, 512.



11 12

19. The use of *o*-xylene, *m*-xylene or naphtalene as co-solvents did not improve the enantioselectivity.
20. a) from NMR studies both on the nitrones and their BF_3-complexes we found that *E*- and *Z*-nitrones can isomerize rapidly in the presence of Lewis acids; b) for references on *Z*-**1**: Koyano, K.; Suzuki, H. *Tetrahedron Lett.* **1968**, 1859; Koyano, K.; Suzuki, H. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 3306; c) for reference on *E*-**1** : Bravo, P.; Bruché, L.; Farina, A.; Fronza, G.; Meille, S.V.; Merli, A. *Tetrahedron : Asymmetry* **1993**, *4*, 2131-2134; d) preparation of BF_3-nitrone complexes: Zeeh, B. *Synthesis*, **1968**, 37; Minkin, V.I.; Medyantseva, E.A.; Andreeva, I.M.; Yureva, V.A. *Zhur. Org. Khim.* **1974**, *10*, 2597; e)*E/Z* stereochemistry: Bjørgo, J.; Boyd, D.R.; Neill, D.C.; Jennings, W.B. *J. Chem. Soc., Chem. Commun.* **1974**, 478-479; Jennings, W.B.; Boyd, D.R.; Waring, L.C. *J. Chem. Soc., Perkin II* **1976**, 610-613; Bjørgo, J.; Boyd, D.R.; Neill, D.C.; Jennings, W.B. *J. Chem. Soc., Perkin I* **1977**, 254.
21. Scheeren, J.W.; Aben, R.W.M.; Ooms, H.J.; Nivard, R.J.F. *J. Org. Chem.* **1977**, *42*, 3128-3132; J.W. Scheeren, "Keten-O,O-acetale" in: Houben-Weyl, 'Methoden der Organischen Chemie', H. Kropf, E. Schaumann (Eds.), Georg Thieme Verlag, Stuttgart, **1993**, Band E15, 1674-1736.
22. Financial support by the Innovation Oriented Research Program (IOP) on Catalysis (no. 90034) of the Netherlands Ministry of Economic Affairs is gratefully acknowledged.

(*Received in UK* 10 *May* 1995)