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1,3-Dipolar Cycloadditions of *N*-Benzyl-2,3-*O*-isopropylidene-D-glyceraldehyde Nitrone to Methoxyallene – Control of Site- and Diastereoselectivity of Isoxazolidine Formation by Lewis Acids

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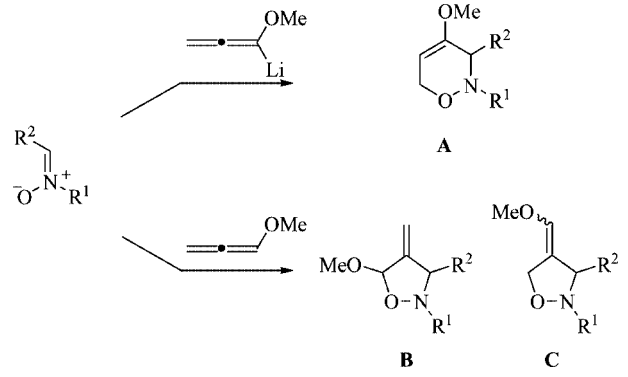
The siteselectivity of cycloadditions of the D-glyceraldehyde-derived nitrone **1** and methoxyallene (**2**) is strongly influenced by Lewis acids. The uncatalyzed reaction results in the formation of isomeric isoxazolidines **3a**–**3d** and **4a**–**4c**, whereas in the presence of different Lewis acids exclusive formation of 4-methylene-substituted isoxazolidines **4a**–**4d** is observed. Furthermore, the diastereofacial selectivity of the methoxyallene addition to nitrone **1** can be controlled, thus giving rise to both diastereomeric isoxazolidines 3,4′-*anti*-**4** or 3,4′-*syn*-**4**, just by employing different Lewis acids. The redox ring-opening of isoxazolidines **4** using Murahashi's protocol yields α-methylene-β-amino acid esters **5a**,**b** and **7a**,**b**.

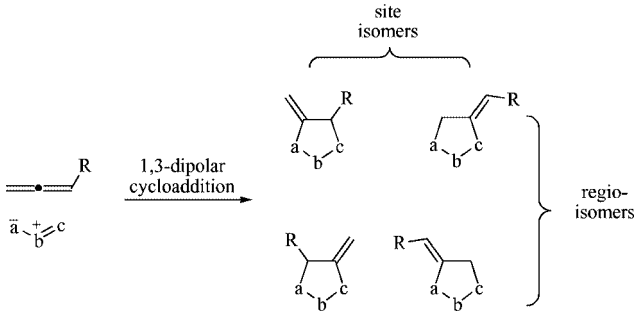
Introduction

Over the years, nitrones have become important building blocks in organic synthesis.[1] Recently, we have published that nitrones are excellent electrophiles for nucleophilic additions of lithiated alkoxyallenes which give rise to the formation of 3,6-dihydro-2*H*-1,2-oxazines **A** (Scheme 1).[2] These heterocycles are extremely versatile intermediates for the synthesis of several classes of enantiopure compounds such as hydroxylated pyrrolidines and azetidines as well as amino polyols.[3]

On the other hand, 1,3-dipolar cycloadditions[4] of nitrones to alkenes are well established reactions by which isoxazolidines are formed, often with a high degree of stereochemical control.[1a,1b] However, allenes as dipolarophiles have attracted less attention in this type of reactions.[5] A possible reason could be that unsymmetrically substituted allenes possess two different double bonds capable of undergoing 1,3-dipolar cycloadditions. Therefore besides regio-, diastereo- and enantioselectivity, also siteselectivity of the reaction has to be considered (Scheme 2). The formation of sixteen isomeric isoxazolidines is conceivable, if nitrones react with monosubstituted allenes. In the literature are so far only few examples on 1,3-dipolar cycloadditions of alkoxyallenes to nitrones.[5b,5c]



Scheme 1. Nucleophilic addition of lithiated methoxyallene to nitrones leading to 1,2-oaxzines **A** and cycloaddition pathways providing isoxazolidiines **B** or **C**.



Scheme 2. Site- and regioselectivity in 1,3-dipolar cycloadditions of nitrones with monosubstituted allenes (stereoisomers are not shown).

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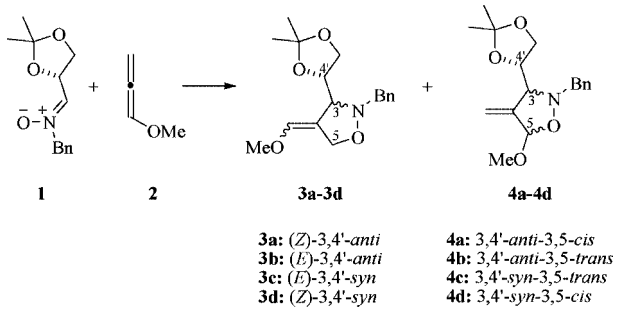
Employment of Lewis acids has extensively been studied during the last two decades, in order to control regio-, diastereo- as well as enantioselectivity of 1,3-dipolar cycloadditions of nitrones.[6] However, the catalytic effect of Lewis acids on the siteselectivity of nitrone cycloadditions to allenes has not been investigated. In the case of a thermal nitrone to methoxyallene cycloaddition it was suggested that the expected 4-methylene-substituted isoxazolidine of type **B** rearranged under the experimental conditions and a 4-methoxymethylene-substituted isoxazolidine of type **C** was formed exclusively.[5b] A 4-methylene-substituted isoxazolidine of type **B** was obtained exclusively in an intramolecular 1,3-dipolar cycloaddition of an allene with a nitrone.[5c] Our objective was to access highly substituted enantiopure isoxazolidines of general structure **B**. We report herein the first Lewis-acid-promoted cycloadditions of D-glyceraldehyde-derived nitrone **1** and methoxyallene (**2**). Nitrone **1** is an easily accessible and important chiral C_3 building block. By its reaction with strong nucleophiles both diastereomeric hydroxylamine derivatives (*anti* and *syn* compounds) are accessible in the presence or absence of Lewis acids.[1c]

Results and Discussion

Due to its enol ether substructure methoxyallene (**2**) can be regarded as an electron-rich π-system. Several reports were recently published dealing with Lewis-acid-catalyzed or -promoted nitrone cycloadditions to electron-rich alkenes. Whereas cycloadditions of simple achiral nitrones bearing *C*-aryl substituents were accelerated in the presence of substoichiometric amounts of catalyst,[7] equimolar amounts of Lewis acids were required in the case of carbohydrate-derived nitrones.[8] Therefore, we decided to study the 1,3-dipolar cycloadditions of D-glyceraldehyde-derived nitrone **1** with **2** in the absence and presence of Lewis acids. The results are summarized in the Table 1. First, the thermal cycloaddition of nitrone **1** and methoxyallene (**2**) has been performed. Nitrone **1** reacted with **2** (Scheme 3) in CH_2Cl_2 at ambient temperature over 72 h to give a mixture of seven of the sixteen theoretically possible isoxazolidines **3a**–**3d** and **4a**–**4c** in 56% overall yield (Table 1, entry 1). Both possible site-isomers have been formed, with 4-methoxymethylene-substituted isoxazolidines **3** being moderately predominant (**3/4** = 77:23).



Scheme 3. 1,3-Dipolar cycloadditions of D-glyceraldehyde-derived nitrone **1** with methoxyallene (**2**).

It has been found, that nitrones are activated for cycloadditions to electron-rich alkenes by coordination to Lewis acids.[7d] Several Lewis acids have been screened in this study (Table 1, entries 2–7). The cycloaddition between **1** and **2** performed in the presence of equimolar amounts of $AlMe_3$ in CH_2Cl_2 was accelerated compared to the uncatalyzed reaction (Table 1, entry 2), moreover, in the crude reaction mixture only 4-methylene-substituted isoxazolidines **4a**–**4d** were detected (56% yield). A similar result was obtained using 1 equiv. of Et_2AlCl in CH_2Cl_2 (Table 1, entry 3). Compared to the $AlMe_3$-promoted reaction, a slightly lower yield (50%) was obtained, but in this particular experiment a lower excess of methoxyallene was used.

Jørgensen et al. have found that the (BINOL)-AlMe complexes catalyze 1,3-dipolar cycloadditions of *C*-aryl-substituted nitrones with vinyl ethers.[7d] In our case, use of 0.2 equiv. of the (*R*)-(BINOL)-AlMe complex resulted in a siteselectivity very similar to the uncatalyzed reaction. Better results were obtained in the presence of 1.0 equiv. of (*R*)- or (*S*)-(BINOL)-AlMe complex, respectively (Table 1, entries 4 and 5). In both cases only isoxazolidines **4** were formed in 44% or 45% yield. Other Lewis acids such as ZnI_2 and TMSOTf were also found to be efficient (Table 1, entries 6 and 7). Whereas the ZnI_2-promoted cycloaddition afforded isoxazolidines **4a**–**4d** in the highest isolated yield (72%), this reaction resulted in a disappointingly poor diastereoselectivity (Table 1, entry 6). The highest rate acceleration was achieved in the reaction with trimethylsilyl triflate (TMSOTf) as promoter in CH_2Cl_2 at –78 to –65 °C. The consumption of nitrone **1** was complete within 1 h and allowed isolation of **4a**–**4d** in 61% yield (Table 1, entry 7).

Table 1. 1,3-Dipolar cycloadditions of D-glyceraldehyde-derived nitrone **1** with methoxyallene (**2**).

	Lewis acid	Conditions[a]	Products[b]	Ratio[c] **4a/4b/4c/4d**	% Yield[d]
1	–	r.t., 72 h[e]	**3a**–**3d**,[f] **4a**–**4c** (77:23)	26:17:57:–	56
2	$AlMe_3$	0 to 8 °C, 50 h[g]	**4a**–**4d**	69:7:22:2	56
3	Et_2AlCl	0 to 8 °C, 51 h	**4a**–**4d**	55:8:32:5	50
4	(*R*)-(BINOL)–AlMe	0 °C to room temp., 27 h	**4a**–**4d**	n.d.	44
5	(*S*)-(BINOL)–AlMe	0 °C to room temp., 27 h	**4a**–**4d**	n.d.	45
6	ZnI_2	0 °C to room temp., 22 h	**4a**–**4d**	17:5:61:17	72
7	TMSOTf	–78 to –65 °C, 1 h	**4a**–**4d**	2:5:65:28	61

[a] 5 equiv. of methoxyallene (**2**), 1 equiv. of Lewis acid and CH_2Cl_2 as solvent were used. [b] Based on ^1H NMR spectra of crude products. [c] Determined by HPLC. [d] Cumulative yield of isolated mixture of isoxazolidines. [e] 2.5 equiv. of methoxyallene (**2**) were employed. [f] Ratio of **3a/3b/3c/3d** = 43:35:8:14. [g] 10 equiv. of methoxyallene (**2**) were used.

FMO theory fails to predict the siteselectivity of the uncatalyzed reaction. DFT[9] calculations (Table 2) suggest that the HOMO of methoxyallene is located at the enol ether moiety, whereas its LUMO is at the terminal double bond. According to the calculated FMO energy gaps, the favoured cycloadduct should be the result of a $LUMO_{nitrone}$–$HOMO_{methoxyallene}$ interaction (ΔE = 5.41 eV); this separation is smaller than that of the other combination: $LUMO_{methoxyallene}$–$HOMO_{nitrone}$ (ΔE = 6.19 eV). Therefore, on the basis of simple FMO theory just regarding the energies of frontier orbitals, methoxyallene (**2**) is expected to undergo the 1,3-dipolar cycloaddition in preference across the more substituted double bond and to produce the 4-methylene-5-methoxy-substituted isoxazolidines **4**, which contradicts the experimentally observed siteselectivity (**3**/**4** = 77:23, Table 1, entry 1). The same disagreement of the theoretically predicted and the observed siteselectivity in methoxyallene cycloadditions towards nitrones has been reported by Padwa et al.[5b] These authors suggested that the 4-methylene-5-methoxy-substituted isoxazolidine of type **B** undergoes a facile rearrangement to give 4-methoxymethylene-substituted isoxazolidines of type **C**. A similar transformation did not occur in our case. After refluxing pure isomer **4c** in toluene for 24 h, no traces of 4-methoxymethylene-substituted isoxazolidines **3** were observed. Hence, the uncatalyzed reaction is apparently controlled by more subtle electronic and by steric effects.

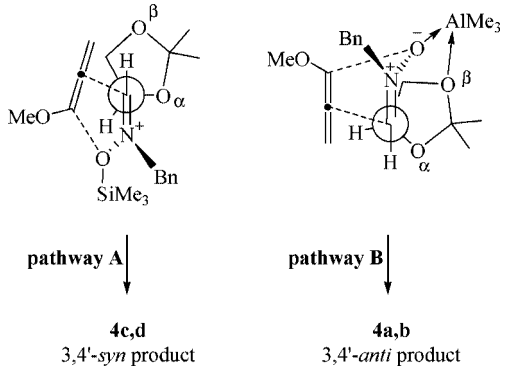
Table 2. Energies of FMOs (in eV) and global indexes: electronic chemical potential (μ, au), chemical hardness (η, au), and global electrophilicity (ω, in eV) of nitrone **1**, nitrone-$AlMe_3$ complex **1**-$AlMe_3$ and methoxyallene (**2**).

	HOMO	LUMO	μ	η	ω
1	–5.98	–0.54	–0.1200	0.1999	0.98
1-$AlMe_3$	–7.42	–1.85	–0.1703	0.2044	1.93
2	–5.95	0.20	–0.1056	0.2262	0.67

The siteselectivity in the presence of $AlMe_3$ is in agreement with the prediction and the cycloaddition is controlled by the $LUMO_{nitrone\ complex}$–$HOMO_{methoxyallene}$ interaction (ΔE = 4.10 eV; $LUMO_{methoxyallene}$–$HOMO_{nitrone\ complex}$ = 7.62 eV).

Recent studies devoted to Diels–Alder[10] and 1,3-dipolar cycloadditions[11] have shown that the global indexes defined in the context of DFT[12] are a powerful tool to understand the behaviour of polar cycloadditions. This model determines the charge transfer pattern and decides which of the partners is acting as nucleophile or electrophile in polar processes. It can also anticipate a concerted pathway in those cases where the electrophilicity/nucleophilicity difference is small.[10,11a] According to this model nitrones are generally classified as moderate electrophiles within the electrophilicity index ω scale and therefore, they can undergo both normal electron-demand ($HOMO_{nitrone}$–$LUMO_{dipolarophile}$) or inverse electron-demand ($LUMO_{nitrone}$–$HOMO_{dipolarophile}$) cycloadditions.[11a] Nitrone **1** has an electrophilicity value ω = 0.98 eV, that also classifies it as moderate electrophile. Coordination of nitrone **1** to $AlMe_3$ strongly increases its electrophilicity from 0.98 to 1.93 eV. A difference of electrophilicity $\Delta\omega$ of the reagent pair has been used as a measure of the polar character of cycloadditions.[10,11a] The $\Delta\omega$ for the reaction between nitrone **1** and methoxyallene has a low value (0.31 eV), thus indicating that the corresponding cycloaddition will have a low polar character. On the other hand, the Lewis-acid-promoted cycloaddition of **1**-$AlMe_3$ and **2** has a value of $\Delta\omega$ = 1.26 eV. This increase of $\Delta\omega$ suggests a more polar process with lower activation energy for the Lewis-acid-promoted reaction. The large increase of $\Delta\omega$ for the catalyzed reaction, accounts for the acceleration of the inverse electron-demand cycloaddition. The increased electrophilic character of the nitrone could also lead to a change of mechanism:[11d] as a consequence of the large electrophilic activation of the nitrone upon coordination of $AlMe_3$, the mechanism of the reaction changes from a concerted asynchronous cycloaddition with a low polar character to a concerted highly asynchronous cycloaddition or even to a stepwise addition with a large polar character.

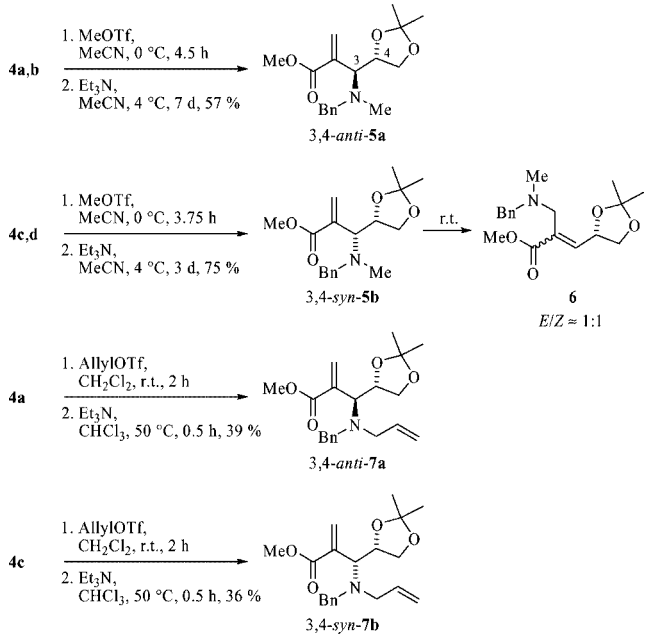
Interestingly, the Lewis acids not only change the siteselectivity of cycloadditions of **1** and **2**, they also considerably influence the diastereoselectivity (Table 1, entries 2, 6 and 7). Precomplexation of nitrone **1** with $AlMe_3$ led to preferential formation of 3,4′-*anti*-**4a**,**b** (3,4′-*anti*-**4a**,**b**/3,4′-*syn*-**4c**,**d** = 76:24). On the other hand, using TMSOTf resulted in a reversal of diastereoselectivity giving 3,4′-*syn*-**4c**,**d** almost exclusively as major isomers (3,4′-*anti*-**4a**,**b**/3,4′-*syn*-**4c**,**d** = 7:93). The facial selectivity seems to depend strongly on the chelating properties of the Lewis acids. The monodentate TMSOTf strongly favours the 3,4′-*syn* products **4c**/**4d**, as expected by the pathway A in Scheme 4 according to the Houk model.[13] Bidentate Lewis acids such as $AlEt_2Cl$ or $AlMe_3$ can additionally coordinate to the oxygen of the dioxolane ring in α- and/or β-position.[14] A β-chelated structure (pathway B, Scheme 4) is preferably adopted in the case of $AlMe_3$, which results in a 3,4′-*anti* stereorelationship (formation of **4a**/**4b**).[14] We can not offer a simple explanation for the *cis*/*trans* selectivity in these cycloadditions which is determined by the preference for one of the two face-to-face approaches of the two prochiral units (methoxyallene and nitrone).



Scheme 4. Pathways of Lewis-acid-promoted cycloadditions of nitrone **1** with methoxyallene.

The relative configuration of C-3 and C-4′ of isoxazolidines **3a**–**3c**, **4a** and **4c** was assigned only tentatively, taking into account already known stereoselectivities of nitrone **1** in additions of nucleophiles[1c] and of other cycloadditions.[15] Assignment of 3,5-*trans* and 3,5-*cis* or *E*- and *Z*-configuration is based on NOE measurements of the isolated isoxazolidines **3a**–**3c**, **4a** and **4c**, respectively.

α-Methylene-β-amino acid derivatives[16] are most directly accessible via aza-Morita–Baylis–Hillman reactions.[17] However, this approach is very substrate dependent and a variety of specific reaction conditions are known for the synthesis of this class of compounds. Therefore, the preparation of highly functionalized α-methylene-β-amino acids is still demanding and the development of alternative methods is an attractive objective in organic synthesis.[18] A variety of reductive isoxazolidine ring-opening methods have been reported, which generate β-amino acids or related derivatives.[19] In our case we have used the redox ring-opening of isoxazolidines first reported by Murahashi et al.[20a] and further employed by others including our groups for the cleavage of N–O heterocycles.[3f,7c,8,20b–20d] Both diastereomers of the corresponding *N*,*N*-disubstituted-α-methylene-β-amino acid ester **5** and **7** were prepared starting from appropriate isoxazolidines **4** and methyl triflate or allyl triflate, respectively (Scheme 5). Treatment of diastereomeric mixtures of isoxazolidines 3,4′-*anti*-**4a**,**b** and 3,4′-*syn*-**4c**,**d** with MeOTf in acetonitrile at 0 °C smoothly afforded the expected *N*-benzyl-*N*-methylisoxazolidinium salts. For the subsequent N–O bond cleavage with triethylamine prolonged reaction times were required. Low temperature was also crucial, in particular for the transformation of 3,4′-*syn*-**4c**,**d** into 3,4′-*syn*-**5b**, while α-methylene-β-amino acid ester 3,4′-*syn*-**5b** underwent further conversion into the thermodynamically more stable product **6** (1:1 mixture of isomers) at room temperature. This process can be explained by an intramolecular Michael addition of the amine moiety, followed by a reverse Michael elimination.[21] Interestingly, a similar transformation was not observed in the case of 3,4′-*anti*-**5a**. *N*-Allylation of **4** with allyl bromide was not successful, probably due to the steric reasons. Reactions of the more reactive allyl triflate with diastereomerically pure 3,4′-*anti*-3,5-*cis*-**4a** or 3,4′-*syn*-3,5-*trans*-**4c** followed by N–O bond cleavage by base treatment led to the formation of the desired *N*-allyl-*N*-benzyl-α-methylene-β-amino acid ester 3,4′-*anti*-**7a** and 3,4′-*syn*-**7b** in moderate 39% and 36% yields, respectively.[22]



Scheme 5. Redox ring-opening of isoxazolidines **4a**–**4d** by treatment with alkylating agents and base.

Conclusions

We have studied the first 1,3-dipolar cycloadditions of D-glyceraldehyde-derived nitrone **1** and methoxyallene (**2**). In the absence of Lewis acid this reaction proceeded essentially unselective to the terminal and to the alkoxysubstituted double bond of methoxyallene, affording seven isomeric isoxazolidines **3a**–**3d** and **4a**–**4c** out of sixteen theoretically possible. We have demonstrated that in the presence of Lewis acids siteselectivity of the cycloaddition was strongly enhanced with the exclusive formation of 4-methylene-substituted isoxazolidines **4a**–**4d**. Furthermore, the diastereofacial selectivity of the methoxyallene addition to the nitrone **1** could be controlled by the nature of the Lewis acid. Precomplexation of nitrone **1** with $AlMe_3$ gave access to isoxazolidines with relative configuration 3,4′-*anti*-**4a**,**b**, whereas 3,4′-*syn*-**4c**,**d** were obtained predominantly in the presence of TMSOTf. The redox ring-opening of isoxazolidines **4** by treatment with reactive alkylating agents such as methyl or allyl triflate resulted in conversion into synthetically valuable α-methylene-β-amino acid esters **5a**,**b** and **7a**,**b**.

Experimental Section

General Methods: Reactions were generally performed under argon in flame-dried flasks, and the components were added by syringe. The starting materials, the D-glyceraldehyde-derived nitrone **1**,[23] methoxyallene[24] and allyl triflate,[25] were prepared according to literature procedures. All other chemicals are commercially available and were used without further purification. Dichloromethane and acetonitrile were distilled from calcium hydride and stored over molecular sieves (4 Å). Products were purified by flash chromatography (FLC) on silica gel (230–400 mesh, Merck). Preparative HPLC was carried out on a Nucleosil 50–5 column and detected with a Knauer variable UV-detector (λ = 255 nm) and a Knauer refractometer. Unless stated otherwise, yields refer to analytically pure samples. Isomer ratios were determined by HPLC. ^{1}H NMR spectra [TMS (δ = 0.00 ppm) as internal standard] and ^{13}C NMR spectra [$CDCl_3$ (δ = 77.0 ppm) as internal standard] were recorded on Jeol Eclipse 500 (500 MHz) and Bruker AC 250 (250 MHz) instruments in $CDCl_3$ solution. Integrals are in accordance with assignments; coupling constants are given in Hz. IR spectra were measured with an FTIR spectrometer Nicolet 5 SXC and 205 (Perkin–Elmer). MS and HRMS analyses were performed on Finnigan MAT 711 (EI, 80 eV, 8 kV), MAT CH7A (EI, 80 eV, 3 kV) instru-

ments. The elemental analyses were recorded with "Elemental-Analyzer" (Vario EL). Optical rotations ($[\alpha]_D$) were determined with Perkin–Elmer 141 or Perkin–Elmer 241 polarimeters at the temperatures given.

All calculations were carried out using PC GAMESS software.[9] Energies of FMOs were obtained from singlepoint DFT calculations using a B3LYP/6-31G* basis set on HF/3-21G*-optimized structures. Global indexes: electronic chemical potential μ, chemical hardness η, and global electrophilicity ω of nitrone **1**, nitrone–$AlMe_3$ complex (**1**-$AlMe_3$), and methoxyallene (**2**) were calculated according to ref.[11a]

Uncatalyzed Cycloaddition: A solution of nitrone **1** (0.500 g, 2.13 mmol) and methoxyallene (**2**, 0.44 mL, 5.3 mmol, 2.5 equiv.) in CH_2Cl_2 (5 mL) was stirred 72 h at room temp. Volatile components were evaporated in vacuo. Preparative HPLC of the residue allowed isolation of isoxazolidines **3a** (72 mg, 11%), **3b** (119 mg, 18%), **3c** (20 mg, 3%), **4a** (21 mg, 3%), **4c** (56 mg, 9%) and a mixture of diastereomers **3a**–**3d** (66 mg, 10%) and **4a**–**4c** (12 mg, 2%).

$AlMe_3$-Promoted Reaction: The reaction was carried out under an argon atmosphere. To a stirred solution of nitrone **1** (0.500 g, 2.13 mmol) in CH_2Cl_2 (5 mL), was added $AlMe_3$ (2 M in hexanes, 1.1 mL, 1 equiv.) at 0 °C and stirring was continued at the same temperature for 1 h. A solution of methoxyallene (**2**, 1.77 mL, 21.3 mmol, 10 equiv.) in CH_2Cl_2 (5 mL) was added in seven portions during 12 h. The temperature was kept between 0 and 8 °C until nitrone **1** was consumed (50 h). The reaction was quenched by addition of MeOH (2 mL) followed by filtration through silica gel and washing with EtOAc/hexane, 1:1. Solvents were evaporated in vacuo and after preparative HPLC of the residue pure isoxazolidines **4a** (240 mg, 37%), **4c** (82 mg, 13%) and a mixture of diastereomers **4a**–**4d** (36 mg, 6%) were isolated.

TMSOTf-Promoted Reaction: The reaction was carried out under an argon atmosphere. To a stirred solution of nitrone **1** (1.00 g, 4.25 mmol) in CH_2Cl_2 (20 mL), was added TMSOTf (0.82 mL, 4.3 mmol, 1 equiv.) at –78 °C. After 20 min, methoxyallene (**2**, 1.77 mL, 21.3 mmol, 5 equiv.) was added dropwise. The temperature was allowed to increase to –65 °C during 1 h. The mixture was again cooled to –78 °C and quenched by addition of 20 mL of saturated $NaHCO_3$. After warming up to room temp., the mixture was extracted with Et_2O, dried with Na_2SO_4 and volatile components were evaporated. Preparative HPLC the of residue allowed isolation of pure isoxazolidines **4a**,**b** (71 mg, 5%), **4c** (483 mg, 37%), 227 mg (17%) of a mixture of **4d**/**4c** (92:8) and 27 mg (2%) of a mixture of all diastereomers **4a**–**4d**.

(3*S*,4*Z*)-2-Benzyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-(methoxymethylene)isoxazolidine (3a): Colourless oil. R_f = 0.30 (EtOAc/hexane, 15:85). $[\alpha]_D$ = +5.6 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.28, 1.32 [2 s, 3 H each, $OC(CH_3)_2O$], 3.60 (dd, *J* = 7.2, 8.6 Hz, 1 H, 5′-H), 3.66 (s, 3 H, OCH_3), 3.64–3.66 (m, 1 H, 3-H), 3.77 (d, *J* = 12.5 Hz, 1 H, NCH_2Ph), 4.00 (dd, *J* = 6.3, 8.6 Hz, 1 H, 5′-H), 4.09 (d, *J* = 12.5 Hz, 1 H, NCH_2Ph), 4.13 (ddd, *J* = 6.0, 6.3, 7.2 Hz, 1 H, 4′-H), 4.39 (ddd, *J* = 1.7, 2.5, 12.5 Hz, 1 H, 5-H), 4.68 (ddd, *J* = 0.7, 2.5, 12.5 Hz, 1 H, 5-H), 6.14 (dt, *J* = 1.1, 2.5 Hz, 1 H, =CH), 7.24–7.38 (m, 5 H, Ph) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.6, 26.5 [2 q, $OC(CH_3)_2O$], 60.1 (q, OCH_3), 60.4 (t, NCH_2Ph), 66.1 (t, C-5′), 66.5 (d, C-3), 66.6 (t, C-5), 76.7 (d, C-4′), 108.9 (s, C-2′), 115.0 (s, C-4), 127.5, 128.4, 129.2, 136.6 (3 d, s, Ph), 141.4 (d, =CH) ppm. IR (film): $\tilde{\nu}$ = 3085 (–2850, =C–H, C–H), 1700 (C=C) cm^{-1}. MS (EI, 80 eV): *m*/*z* (%) = 305 (<1) [M^+], 290 (2) [M – CH_3]$^+$, 274 (<1) [M – CH_3O]$^+$, 204 (60) [M – $C_5H_9O_2$]$^+$, 101 (3) [$C_5H_9O_2$]$^+$, 91 (100) [C_7H_7]$^+$. HRMS: (EI, 80 eV) calcd. for $C_{16}H_{20}NO_4$ 290.13922 [M – CH_3]$^+$; found 290.13892. $C_{17}H_{23}NO_4$ (305.4): calcd. C 66.86, H 7.59; N 4.59; found C 66.90, H 7.59, N 4.54.

(3*S*,4*E*)-2-Benzyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-(methoxymethylene)isoxazolidine (3b): Colourless wax. R_f = 0.14 (EtOAc/hexane, 15:85). $[\alpha]_D$ = +20.5 (*c* = 1.06, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.25, 1.32 [2 s, 3 H each, $OC(CH_3)_2O$], 3.63 (s, 3 H, OCH_3), 3.80 (d, *J* = 12.7 Hz, 1 H, NCH_2Ph), 3.83–3.85 (m, 1 H, 3-H), 3.89, 3.91 (2 dd, *J* = 6.3, 9.4 Hz, 1 H each, 5′-H), 4.06 (d, *J* = 12.7 Hz, 1 H, NCH_2Ph), 4.12 (td, *J* = 6.3, 8.1 Hz, 1 H, 4′-H), 4.38 (ddd, *J* = 1.5, 2.1, 10.7 Hz, 1 H, 5-H), 4.53 (ddd, *J* = 0.7, 1.8, 10.7 Hz, 1 H, 5-H), 6.22 (dt, *J* = 1.5, 1.8 Hz, 1 H, =CH), 7.22–7.26, 7.29–7.32, 7.38–7.40 (3 m, 5 H, Ph) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.5, 26.5 [2 q, $OC(CH_3)_2O$], 59.9 (q, OCH_3), 60.6 (t, NCH_2Ph), 66.4, 66.5 (2 t, C-5, C-5′), 67.0 (d, C-3), 76.3 (d, C-4′), 109.1 (s, C-2′), 115.4 (s, C-4), 127.2, 128.2, 129.3, 136.7 (3 d, s, Ph), 141.4 (d, =CH) ppm. IR (film): $\tilde{\nu}$ = 3085 –2845 (=C–H, C–H), 1700 (C=C) cm^{-1}. MS (EI, 80 eV): *m*/*z* (%) = 305 (<1) [M^+], 290 (<1) [M – CH_3]$^+$, 204 (33) [M – $C_5H_9O_2$]$^+$, 101 (4) [$C_5H_9O_2$]$^+$, 91 (100) [C_7H_7]$^+$. HRMS: (EI, 80 eV) calcd. for $C_{16}H_{20}NO_4$ 290.13922 [M – CH_3]$^+$; found 290.13839. $C_{17}H_{23}NO_4$ (305.4): calcd. C 66.86, H 7.59, N 4.59; found C 66.74, H 7.73, N 4.46.

(3*R*,4*E*)-2-Benzyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-(methoxymethylene)isoxazolidine (3c): Colourless oil. R_f = 0.20 (EtOAc/hexane, 15:85). $[\alpha]_D$ = –38.0 (*c* = 1.03, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.33, 1.42 [2 s, 3 H each, $OC(CH_3)_2O$], 3.63 (s, 3 H, OCH_3), 3.83 (d, *J* = 12.9 Hz, 1 H, NCH_2Ph), 3.89 (m_c, 2 H, 5′-H, 3-H), 3.98 (d, *J* = 12.9 Hz, 1 H, NCH_2Ph), 4.00 (dd, *J* = 6.4, 8.4 Hz, 1 H, 5′-H), 4.24 (dt, *J* = 5.7, 6.4 Hz, 1 H, 4′-H), 4.40 (ddd, *J* = 1.7, 1.8, 10.5 Hz, 1 H, 5-H), 4.51 (ddd, *J* = 0.8, 1.8, 10.5 Hz, 1 H, 5-H), 6.23 (q, *J* = 1.8 Hz, 1 H, =CH), 7.24–7.37 (m, 5 H, Ph) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.4, 26.5 [2 q, $OC(CH_3)_2O$], 59.9 (q, OCH_3), 61.4 (t, NCH_2Ph), 66.5 (d, C-3), 66.6 (t, C-5′), 66.9 (t, C-5), 76.1 (d, C-4′), 109.3 (s, C-2′), 116.3 (s, C-4), 127.4, 128.3, 129.1, 137.1 (3 d, s, Ph), 141.1 (d, =CH) ppm. IR (film): $\tilde{\nu}$ = 3090 –2840 (=C–H, C–H), 1705 (C=C) cm^{-1}. MS (EI, 80 eV): *m*/*z* (%) = 305 (1) [M^+], 290 (3) [M – CH_3]$^+$, 204 (100) [M – $C_5H_9O_2$]$^+$, 101 (6) [$C_5H_9O_2$]$^+$, 91 (167) [C_7H_7]$^+$. $C_{17}H_{23}NO_4$ (305.4): calcd. C 66.86, H 7.59; N 4.59; found C 66.57, H 7.15, N 4.52.

(3*R*,4*Z*)-2-Benzyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-(methoxymethylene)isoxazolidine (3d): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.31, 1.36 [2 s, 3 H each, $OC(CH_3)_2O$], 3.34 (d_{br}, *J* = 8.7 Hz, 1 H, 3-H), 3.61 (dd, *J* = 4.8, 8.7 Hz, 1 H, 5′-H), 3.69 (s, 3 H, OCH_3), 3.72 (d, *J* = 12.5 Hz, 1 H, NCH_2Ph), 3.95 (ddd, *J* = 4.8, 6.2, 8.7 Hz, 1 H, 4′-H), 4.03 (d, *J* = 12.5 Hz, 1 H, NCH_2Ph), 4.04 (dd, *J* = 6.2, 8.7 Hz, 1 H, 5′-H), 4.49 (ddd, *J* = 1.6, 2.5, 12.3 Hz, 1 H, 5-H), 4.70 (ddd, *J* = 0.6, 2.5, 12.3 Hz, 1 H, 5-H), 6.16 (dt, *J* = 0.9, 2.5 Hz, 1 H, =CH), 7.27–7.37 (m, 5 H, Ph) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.2, 27.0 [2 q, $OC(CH_3)_2O$], 60.1 (q, OCH_3), 60.3 (t, NCH_2Ph), 66.3 (t, C-5′), 67.9 (d, C-3), 67.9 (t, C-5), 76.2 (d, C-4′), 109.2 (s, C-2′), 116.1 (s, C-4), 127.6, 128.4, 129.2, 136.6 (3 d, s, Ph), 141.4 (d, =CH) ppm.

(3*S*,5*R*)-2-Benzyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-5-methoxy-4-methyleneisoxazolidine (4a): Colourless oil. R_f = 0.48 (EtOAc/hexane, 15:85). $[\alpha]_D$ = –132.0 (*c* = 1.02, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.34, 1.38 [2 d, *J* = 0.5 Hz, 3 H each, $OC(CH_3)_2O$], 3.35 (s, 3 H, OCH_3), 3.64 (td, *J* = 2.3, 5.3 Hz, 1 H, 3-H), 4.00 (d, *J* = 14.0 Hz, 1 H, NCH_2Ph), 4.02, 4.04 (2 dd, *J* = 6.4, 8.4 Hz, 1 H each, 5′-H), 4.29 (d, *J* = 14.0 Hz, 1 H, NCH_2Ph), 4.41 (dt, *J* = 5.3, 6.4 Hz, 1 H, 4′-H), 5.24–5.25 (m, 2 H, 5-H, =CH_2), 5.37 (dd, *J* = 1.0, 2.3 Hz, 1 H, =CH_2), 7.24–7.27, 7.30–

7.34, 7.40–7.42 (3 m, 5 H, Ph) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.1, 26.5 [2 q, OC(CH_3)$_2$O], 54.8 (q, OCH_3), 63.2 (t, NCH_2Ph), 65.9 (t, C-5′), 66.9 (d, C-3), 77.0 (d, C-4′), 102.2 (d, C-5), 109.3 (s, C-2′), 111.5 (t, =CH_2), 127.2, 128.2, 128.7, 137.3 (3 d, s, Ph), 148.8 (s, C-4) ppm. IR (film): $\tilde{\nu}$ = 3090 –2830 (=C–H, C–H), 1675 (C=C), 1605, 1585 [C=C (Ph)] cm^{-1}. MS (EI, 80 eV): *m*/*z* (%) = 305 (7) [M$^+$], 290 (5) [M – CH_3]$^+$, 274 (2) [M – OCH_3]$^+$, 246 (<1) [M – $C_2H_3O_2$]$^+$, 216 (2) [$C_{14}H_{18}NO$]$^+$, 204 (51) [M – $C_5H_9O_2$]$^+$, 101 (8) [$C_5H_9O_2$]$^+$, 91 (100) [C_7H_7]$^+$. HRMS: (EI, 80 eV) calcd. for $C_{17}H_{23}NO_4$ 305.16272; found 305.16377. $C_{17}H_{23}NO_4$ (305.4): calcd. C 66.86, H 7.59, N 4.59; found C 66.89, H 7.68, N 4.59.

(3*S*,5*S*)-2-Benzyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-5-methoxy-4-methyleneisoxazolidine (4b): The following characteristic signals can be unambiguously assigned: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.31, 1.38 [2 s, 3 H each, OC(CH_3)$_2$O], 3.45 (s, 3 H, OCH_3), 4.36 (d, *J* = 12.6 Hz, 1 H, NCH_2Ph), 5.33–5.34 (m, 1 H, 5-H), 5.54–5.56 (m, 2 H, =CH_2) ppm.

(3*R*,5*R*)-2-Benzyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-5-methoxy-4-methylenesoxazolidine (4c): Colourless oil. R_f = 0.40 (EtOAc/hexane, 15:85). [α]$_D$ = +178.4 (*c* = 1.09, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.32, 1.36 [2 d, *J* = 0.5 Hz, 3 H each, OC(CH_3)$_2$O], 3.37 (s, 3 H, OCH_3), 3.55 (td, *J* = 2.2, 7.1 Hz, 1 H, 3-H), 3.91 (dd, *J* = 7.1, 8.3 Hz, 1 H, 5′-H), 4.07 (dd, *J* = 6.4, 8.3 Hz, 1 H, 5′-H), 4.08 (d, *J* = 13.9 Hz, 1 H, NCH_2Ph), 4.24 (td, *J* = 7.1, 6.4 Hz, 1 H, 4′-H), 4.27 (d, *J* = 13.9 Hz, 1 H, NCH_2Ph), 5.20 (br. s, 1 H, 5-H), 5.25, 5.35 (2 dd, *J* = 1.3, 2.2 Hz, 1 H each, =CH_2), 7.24–7.27, 7.30–7.33, 7.40–7.41 (3 m, 5 H, Ph) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.1, 26.5 [2 q, OC(CH_3)$_2$O], 54.9 (q, OCH_3), 62.2 (t, NCH_2Ph), 66.5 (t, C-5′), 68.5 (d, C-3), 76.0 (d, C-4′), 102.4 (d, C-5), 109.2 (s, C-2′), 112.0 (t, =CH_2), 127.2, 128.2, 129.1, 136.8 (3 d, s, Ph), 148.2 (s, C-4) ppm. IR (film): $\tilde{\nu}$ = 3090 –2830 (=C–H, C–H), 1675 (C=C), 1605, 1585 [C=C (Ph)] cm^{-1}. MS (EI, 80 eV): *m*/*z* (%) = 305 (6) [M$^+$], 290 (5) [M – CH_3]$^+$, 274 (2) [M – OCH_3]$^+$, 247 (1) [M – C_3H_6O]$^+$, 216 (1) [$C_{14}H_{18}NO$]$^+$, 204 (54) [M – $C_5H_9O_2$]$^+$, 101 (6) [$C_5H_9O_2$]$^+$, 91 (100) [C_7H_7]$^+$. HRMS: (EI, 80 eV) calcd. for $C_{17}H_{23}NO_4$ 305.16272; found 305.16355. $C_{17}H_{23}NO_4$ (305.4): calcd. C 66.86, H 7.59, N 4.59; found C 66.77, H 7.42, N 4.55.

(3*R*,5*S*)-2-Benzyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-5-methoxy-4-methyleneisoxazolidine (4d): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.27, 1.32 [2 s, 3 H each, OC(CH_3)$_2$O], 3.47 (s, 3 H, OCH_3), 3.60 (dd, *J* = 7.0, 8.6 Hz, 1 H, 5′-H), 3.80–3.82 (m, 1 H, 3-H), 3.99 (dd, *J* = 6.3, 8.6 Hz, 1 H, 5′-H), 4.08 (d, *J* = 12.7 Hz, 1 H, NCH_2Ph), 4.13 (dt, *J* = 6.3, 7.0 Hz, 1 H, 4′-H), 4.40 (d, *J* = 12.7 Hz, 1 H, NCH_2Ph), 5.30 (dt, *J* = 1.5, 2.8 Hz, 1 H, 5-H), 5.51, 5.57 (2 t, *J* = 1.5 Hz, 1 H each, =CH_2), 7.25–7.28, 7.31–7.34, 7.38–7.39 (3 m, 5 H, Ph) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.5, 26.3 [2 q, OC(CH_3)$_2$O], 55.9 (q, OCH_3), 64.1 (t, NCH_2Ph), 65.9 (t, C-5′), 68.1 (d, C-3), 76.7 (d, C-4′), 106.0 (d, C-5), 109.0 (s, C-2′), 114.6 (t, =CH_2), 127.4, 128.3, 129.1, 137.0 (3 d, s, Ph), 148.4 (s, C-4) ppm.

***N*-Methylation and Redox Cleavage of Isoxazolidines:** The corresponding isoxazolidine **4** (as diastereomeric mixture of 3,5-*cis*/3,5-*trans*, 0.100 g, 0.33 mmol) was dissolved in acetonitrile (2 mL). The solution was treated with methyl triflate (0.041 mL, 0.36 mmol, 1.1 equiv.) at 0 °C and the resulting mixture was stirred at 0 °C for the time given in the individual experiments until the starting material was consumed. The mixture was then treated with triethylamine (0.137 mL, 0.98 mmol, 3 equiv.) and stirred for the given time until the isoxazolidinium salt disappeared (tlc control). After all volatile components had been removed the residue was dissolved in water and extracted with hexane, dried with Na_2SO_4 and concentrated in vacuo. For purification FLC on silica gel (EtOAc/hexane, 15:85) was employed.

Methyl 3-[Benzyl(methyl)amino]-2,3-dideoxy-2-methylene-4,5-*O*-(1-methylethylidene)-D-*erythro*-pentanoate (5a): According to the general procedure above, the mixture was treated with MeOTf at 0 °C for 4.5 h and then with Et_3N at 0 to 4 °C for 7 d. After FLC 60 mg (57%) of **5a** (yellow oil) was isolated. R_f = 0.52 (EtOAc/hexane, 15:85). [α]$_D$ = +51.1 (*c* = 1.09, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.35, 1.37 [2 s, 3 H each, OC(CH_3)$_2$O], 2.08 (s, 3 H, NCH_3), 3.50, 3.53 (2 d, *J* = 13.5 Hz, 1 H each, NCH_2Ph), 3.79 (s, 3 H, $COOCH_3$), 3.85 (d, *J* = 9.6 Hz, 1 H, 3-H), 4.01, 4.20 (2 dd, *J* = 6.0, 8.4 Hz, 1 H each, 5-H), 4.50 (td, *J* = 6.0, 9.6 Hz, 1 H, 4-H), 5.78 (br. s, 1 H, =CH_2), 6.58 (d, *J* = 0.8 Hz, 1 H, =CH_2), 7.21–7.26 (m, 3 H, Ph), 7.28–7.31 (m, 2 H, Ph) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.6, 26.8 [2 q, OC(CH_3)$_2$O], 37.8 (q, NCH_3), 52.0 (q, $COOCH_3$), 59.2 (t, NCH_2Ph), 68.7 (t, C-5), 65.1 (d, C-3), 75.1 (d, C-4), 109.3 [s, O*C*(CH_3)$_2$O], 126.9, 128.2 (2 d, Ph), 128.3 (t, =CH_2), 128.4, 135.5, 139.5 (d, 2 s, Ph, C-2), 168.1 (s, $COOCH_3$) ppm. IR (film): $\tilde{\nu}$ = 3105–2795 (=C–H, C–H), 1720 (C=O), 1625 (C=C), 1600, 1585 [C=C (Ph)] cm^{-1}. MS (EI, 80 eV): *m*/*z* (%) = 319 (3) [M$^+$], 304 (6) [M – CH_3]$^+$, 288 (<1) [M – OCH_3]$^+$, 218 (64) [M – $C_5H_9O_2$]$^+$, 101 (5) [$C_5H_9O_2$]$^+$, 91 (100) [C_7H_7]$^+$. $C_{18}H_{25}NO_4$ (319.4): calcd. C 67.69, H 7.89; N 4.39; found C 67.54, H 7.93, N 4.40.

Methyl 3-[Benzyl(methyl)amino]-2,3-dideoxy-2-methylene-4,5-*O*-(1-methylethylidene)-D-*threo*-pentanoate (5b): According to the general procedure above, the mixture was treated with MeOTf at 0 °C for 3.75 h and then with Et_3N at 0 to 4 °C for 3 d. After FLC 79 mg (75%) of **5b** (yellowish oil) was isolated. R_f = 0.43 (EtOAc/hexane, 15:85). [α]$_D$ = –33.5 (*c* = 0.98, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.40, 1.43 [2 s, 3 H each, OC(CH_3)$_2$O], 2.24 (s, 3 H, NCH_3), 3.57 (dd, *J* = 7.2, 8.2 Hz, 1 H, 5-H), 3.60 (d, *J* = 13.5 Hz, 1 H, NCH_2Ph), 3.77 (s, 3 H, $COOCH_3$), 3.79 (dd, *J* = 1.0, 8.8 Hz, 1 H, 3-H), 3.80 (d, *J* = 13.5 Hz, 1 H, NCH_2Ph), 3.98 (dd, *J* = 6.4, 8.2 Hz, 1 H, 5-H), 4.62 (ddd, *J* = 6.4, 7.2, 8.8 Hz, 1 H, 4-H), 5.57 (t, *J* = 1.0 Hz, 1 H, =CH_2), 6.31 (d, *J* = 1.0 Hz, 1 H, =CH_2), 7.20–7.23, 7.27–7.33 (2 m, 5 H, Ph) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.5, 26.7 [2 q, OC(CH_3)$_2$O], 37.5 (q, NCH_3), 52.1 (q, $COOCH_3$), 59.3 (t, NCH_2Ph), 65.0 (d, C-3), 67.5 (t, C-5), 75.4 (d, C-4), 109.7 [s, O*C*(CH_3)$_2$O], 126.2 (t, CH_2), 126.7, 128.1, 128.7, 138.0, 139.8 (3 d, 2 s, Ph, C-2), 167.7 (s, $COOCH_3$) ppm. IR (Film): $\tilde{\nu}$ = 3105–2790 (=C–H, C–H), 1720 (C=O), 1650 (C=C), 1600, 1585 [C=C (Ph)] cm^{-1}. MS (EI, 80 eV): *m*/*z* (%) = 319 (7) [M$^+$], 304 (19) [M – CH_3]$^+$, 288 (<1) [M – OCH_3]$^+$, 218 (50) [M – $C_5H_9O_2$]$^+$, 101 (4) [$C_5H_9O_2$]$^+$, 91 (100) [C_7H_7]$^+$. $C_{18}H_{25}NO_4$ (319.4): calcd. C 67.69, H 7.89; N 4.39; found C 67.15, H 7.38, N 4.32.

Methyl (2*E*/2*Z*)-2-{[Benzyl(methyl)amino]methyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]}acrylate (6): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.39, 1.45, 1.46 [3 s, 3 H, 1.5 H each, OC(CH_3)$_2$O], 2.12, 2.17 (2 s, 1.5 H each, NCH_3), 3.05 (dd, *J* = 1.1, 13.8 Hz, 0.5 H, 1′-H), 3.20 (d, *J* = 12.8 Hz, 0.5 H, 1′-H), 3.27 (dd, *J* = 0.9, 12.8 Hz, 0.5 H, 1′-H), 3.33 (td, *J* = 1.1, 13.8 Hz, 0.5 H, 1′-H), 3.43, 3.46, 3.54, 3.55 (4 d, *J* = 13.0, 13.2 Hz, 0.5 H each, NCH_2Ph), 3.61 (dd, *J* = 6.8, 8.3 Hz, 0.5 H, 5-H), 3.62 (dd, *J* = 7.3, 8.5 Hz, 0.5 H, 5-H), 3.74, 3.75 (2 s, 1.5 H each, $COOCH_3$), 4.18 (dd, *J* = 6.5, 8.2 Hz, 0.5 H, 5-H), 4.31 (dd, *J* = 6.8, 8.3 Hz, 0.5 H, 5-H), 4.93 (ddd, *J* = 6.5, 7.3, 8.5 Hz, 0.5 H, 4-H), 5.17 (q, *J* = 6.8 Hz, 0.5 H, 4-H), 6.21 (td, *J* = 1.1, 6.8 Hz, 0.5 H, 3-H), 6.81 (dd, *J* = 0.9, 8.5 Hz, 0.5 H, 3-H), 7.28 (m, 5 H, Ph) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.5, 25.7, 26.6 [3 q, OC(CH_3)$_2$O], 41.7, 42.0 (2 q, NCH_3), 51.7, 52.0 (2 q, $COOCH_3$), 52.4, 59.5 (2 t, C-1′), 61.9, 62.5

(2 t, NCH_2Ph), 68.9, 69.7 (2 t, C-5), 72.5, 73.9 (2 d, C-4), 109.6, 109.9 [2 s, O$C(CH_3)_2$O], 127.0, 127.1, 128.1, 128.2, 128.9, 129.1, 131.8, 132.4, 138.7, 138.9 (6 d, 4 s, C-2, Ph), 142.1, 142.7 (2 d, C-3), 167.2, 167.6 (2 s, $COOCH_3$) ppm.

***N*-Allylation and Redox Cleavage of Isoxazolidines:** Freshly prepared allyl triflate (1 M in CCl_4, 0.43 mL, 1.5 equiv., filtered from AgI) was added at 0 °C under an argon atmosphere to a stirred CH_2Cl_2 solution of the corresponding isoxazolidine **4a** or **4c** (0.100 g, 0.33 mmol), the temperature was raised and stirring continued for 2 h at room temp. Solvents were evaporated, the residue was dissolved in $CHCl_3$ (5 mL), Et_3N (0.09 mL, 0.7 mmol, 2 equiv.) was added and the mixture was heated 30 min at 50 °C. After all volatile materials had been removed the residue was dissolved in water and extracted with hexane, dried with Na_2SO_4 and concentrated in vacuo. For purification FLC on silica gel (CH_2Cl_2/EtOAc/hexane = 30:3.5:66.5) was employed.

Methyl 3-[Allyl(benzyl)amino]-2,3-dideoxy-2-methylene-4,5-*O*-(1-methylethylidene)-D-*erythro*-pentanoate (7a): After FLC 44 mg (39%) of **7a** (colourless oil) and 14 mg (14%) of starting isoxazolidines **4a**,**b** were isolated. R_f = 0.51 (EtOAc/hexane, 10:90). $[a]_D$ = +81.4 (c = 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.30, 1.31 [2 s, 3 H each, $OC(CH_3)_2O$], 2.91 (tdd, J = 1.2, 7.8, 14.2 Hz, 1 H, NCH_2), 3.18 (tdd, J = 1.7, 5.1, 14.2 Hz, 1 H, NCH_2), 3.33, 3.79 (2 d, J = 14.0 Hz, 1 H each, NCH_2Ph), 3.79 (s, 3 H, $COOCH_3$), 3.84 (d, J = 9.8 Hz, 1 H, 3-H), 3.85, 4.13 (2 dd, J = 6.2, 8.4 Hz, 1 H each, 5-H), 4.51 (td, J = 6.2, 9.8 Hz, 1 H, 4-H), 5.11 (dddd, J = 1.2, 1.7, 1.9, 10.1 Hz, 1 H, CH=CH_2), 5.15 (dddd, J = 1.2, 1.7, 1.9, 18.0 Hz, 1 H, CH=CH_2), 5.75 (d, J = 1.0 Hz, 1 H, 2-CH_2), 5.75 (dddd, J = 5.1, 7.8, 10.1, 18.0 Hz, 1 H, CH=CH_2), 6.54 (d, J = 1.0 Hz, 1 H, 2-CH_2), 7.21–7.32 (m, 5 H, Ph) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.7, 26.7 [2 q, $OC(CH_3)_2O$], 52.0 (q, $COOCH_3$), 54.0 (t, N-CH_2), 54.6 (t, NCH_2Ph), 61.5 (d, C-3), 68.8 (t, C-5), 75.0 (d, C-4), 109.2 [s, O$C(CH_3)_2$O], 117.5 (t, CH=CH_2), 126.9, 128.2, 128.5 (3 d, Ph), 128.8 (t, 2-CH_2), 136.0, 136.6 (2 s, Ph, C-2), 139.8 (d, CH=CH_2), 168.1 (s, $COOCH_3$) ppm. IR (film): $\tilde{\nu}$ = 3085–2815 (=C–H, C–H), 1720 (C=O), 1640, 1625 (C=C), 1600, 1585 [C=C (Ph)] cm^{-1}. MS (EI, 80 eV): m/z (%) = 345 (< 1) [M$^+$], 330 (3) [M – CH_3]$^+$, 314 (<1) [M – OCH_3]$^+$, 244 (100) [M – $C_5H_9O_2$]$^+$, 91 (65) [C_7H_7]$^+$. $C_{20}H_{27}NO_4$ (345.4): calcd. C 69.54, H 7.88; N 4.05; found C 69.52, H 7.97, N 3.98.

Methyl 3-[Allyl(benzyl)amino]-2,3-dideoxy-2-methylene-4,5-*O*-(1-methylethylidene)-D-*threo*-pentanoate (7b): After FLC 41 mg (36%) of **7b** (colourless oil) and 42 mg (42%) of unreacted starting isoxazolidine **4c** were isolated. R_f = 0.51 (EtOAc/hexane, 10:90). $[a]_D$ = –31.3 (c = 1.02, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.38, 1.42 [2 s, 3 H each, $OC(CH_3)_2O$], 3.08, 3.40 (2 tdd, J = 1.5, 6.4, 14.1 Hz, 1 H each, NCH_2), 3.56 (dd, J = 7.4, 8.2 Hz, 1 H, 5-H), 3.65 (d, J = 13.9 Hz, 1 H, NCH_2Ph), 3.74 (s, 3 H, $COOCH_3$), 3.85 (d, J = 13.9 Hz, 1 H, NCH_2Ph), 3.90 (dd, J = 0.8, 8.3 Hz, 1 H, 3-H), 3.93 (dd, J = 6.4, 8.2 Hz, 1 H, 5-H), 4.58 (ddd, J = 6.4, 7.4, 8.3 Hz, 1 H, 4-H), 5.07 (tdd, J = 1.5, 2.3, 10.1 Hz, 1 H, CH=CH_2), 5.13 (tdd, J = 1.5, 2.3, 16.6 Hz, 1 H, CH=CH_2), 5.58 (s, 1 H, 2-CH_2), 5.84 (tdd, J = 6.4, 10.1, 16.6 Hz, 1 H, CH=CH_2), 6.25 (d, J = 0.8 Hz, 1 H, 2-CH_2), 7.19–7.21, 7.25–7.28, 7.31–7.33 (3 m, 5 H, Ph) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.4, 26.6 [2 q, $OC(CH_3)_2O$], 52.0 (q, $COOCH_3$), 53.6 (t, N-CH_2), 54.1 (t, NCH_2Ph), 60.9 (d, C-3), 67.7 (t, C-5), 76.0 (d, C-4), 109.5 [s, O$C(CH_3)_2$O], 116.8 (t, CH=CH_2), 126.1 (t, 2-CH_2), 126.6, 128.0, 128.7, 137.0, 139.0 (3 d, 2 s, Ph, C-2), 140.3 (d, CH=CH_2), 167.9 (s, $COOCH_3$) ppm. IR (Film): $\tilde{\nu}$ = 3085–2810 (=C–H, C–H), 1725 (C=O), 1640, 1625 (C=C), 1600, 1585 [C=C (Ph)] cm^{-1}. MS (EI, 80 eV): m/z (%) = 345 (1) [M$^+$], 330 (4) [M – CH_3]$^+$, 314 (<1) [M – OCH_3]$^+$, 244 (90) [M – $C_5H_9O_2$]$^+$, 91 (100) [C_7H_7]$^+$. $C_{20}H_{27}NO_4$ (345.4): calcd. C 69.54, H 7.88; N 4.05; found C 69.37, H 7.70, N 3.92.

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[1] For reviews on 1,3-dipolar cycloadditions of nitrones see: a) J. J. Tufariello in *1,3-Dipolar Cycloaddition Chemistry* (Ed.: A. Padwa), Wiley-Interscience, New York, **1984**, vol. 2, chapter 9, pp. 83–168; b) R. C. F. Jones, J. N. Martin in *The Chemistry of Heterocyclic Compounds*, vol. 59: *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products* (Eds.: A. Padwa, W. H. Pearson), John Wiley & Sons, New York, **2002**, chapter 1, pp. 1–81; for reviews on nucleophilic additions to nitrones see: c) P. Merino, S. Franco, F. L. Merchán, T. Tejero, *Synlett* **2000**, 442–454; d) F. Cardona, A. Goti, *Angew. Chem.* **2005**, *117*, 8042–8045; *Angew. Chem. Int. Ed.* **2005**, *44*, 7832–7835.

[2] a) W. Schade, H.-U. Reißig, *Synlett* **1999**, 632–634; b) R. Pulz, S. Cicchi, A. Brandi, H.-U. Reißig, *Eur. J. Org. Chem.* **2003**, 1153–1156; c) M. Helms, W. Schade, R. Pulz, T. Watanabe, A. Al-Harrasi, L. Fišera, I. Hlobilová, G. Zahn, H.-U. Reißig, *Eur. J. Org. Chem.* **2005**, 1003–1019.

[3] a) R. Pulz, T. Watanabe, W. Schade, H.-U. Reißig, *Synlett* **2000**, 983–986; b) R. Pulz, A. Al-Harrasi, H.-U. Reißig, *Synlett* **2002**, 817–819; c) R. Pulz, A. Al-Harrasi, H.-U. Reißig, *Org. Lett.* **2002**, *4*, 2353–2355; d) R. Pulz, W. Schade, H.-U. Reißig, *Synlett* **2003**, 405–407; e) M. Helms, H.-U. Reißig, *Eur. J. Org. Chem.* **2005**, 998–1001; f) A. Al-Harrasi, H.-U. Reißig, *Synlett* **2005**, 1152–1154; g) A. Al-Harrasi, H.-U. Reißig, *Angew. Chem. Int. Ed.* **2005**, *44*, 6227–6231; *Angew. Chem.* **2005**, *117*, 6383–6387; h) A. Al-Harrasi, H.-U. Reißig, *Synlett* **2005**, 2376–2378; i) F. Pfrengle, A. Al-Harrasi, H.-U. Reißig, *Synlett* **2006**, 3498–3500; j) B. Bressel, B. Egart, A. Al-Harrasi, R. Pulz, H.-U. Reißig, I. Brüdgam, *Eur. J. Org. Chem.* **2007**, in press. For the synthetic use of other 1,2-oxazine derivatives see: R. Zimmer, H.-U. Reißig, *Angew. Chem.* **1988**, *100*, 1576–1577; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1518–1519; H.-U. Reißig, C. Hippeli, T. Arnold, *Chem. Ber.* **1990**, *123*, 2403–2411 and references cited therein.

[4] R. Huisgen, *Angew. Chem.* **1963**, *75*, 604–637; *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 321–406.

[5] a) M. Murakami, T. Matsuda in *Modern Allene Chemistry* (Eds.: N. Krause, A. S. K. Hashmi), Wiley-VCH, Weinheim, **2004**, vol. 2, chapter 12, pp. 727–815; b) A. Padwa, W. H. Bullock, D. N. Kline, J. Perumattam, *J. Org. Chem.* **1989**, *54*, 2862–2869; c) A. Padwa, M. Meske, Z. Ni, *Tetrahedron Lett.* **1993**, *34*, 5047–5050; d) A. Piperno, A. Rescifina, A. Corsaro, M. A. Chiacchio, A. Procopio, R. Romeo, *Eur. J. Org. Chem.* **2007**, 1517–1521; e) G. Broggini, G. Zecchi, *Gazz. Chim. Ital.* **1996**, *126*, 479–488; f) A. Padwa, M. Matzinger, Y. Tomioka, M. K. Venkatramanan, *J. Org. Chem.* **1988**, *53*, 955–963; g) P. Parpani, G. Zecchi, *J. Org. Chem.* **1987**, *52*, 1417–1421; h) W. R. Dolbier Jr, G. E. Wicks, C. R. Burkholder, *J. Org. Chem.* **1987**, *52*, 2196–2201.

[6] a) K. V. Gothelf, S. Kanemasa, K. A. Jørgensen in *Cycloaddition Reactions in Organic Synthesis* (Eds.: S. Kobayashi, K. A. Jørgensen), Wiley-VCH, Weinheim, **2001**, pp. 211–326; b) K. V. Gothelf, K. A. Jørgensen, *Chem. Rev.* **1998**, *98*, 863–909.

[7] a) J.-P. G. Seerden, M. M. M. Kuypers, H. W. Scheeren, *Tetrahedron: Asymmetry* **1995**, *6*, 1441–1450; b) J.-P. G. Seerden, M. M. M. Kuypers, H. W. Scheeren, *Tetrahedron* **1997**, *53*, 11843–11852; c) M. J. Meske, *J. Prakt. Chem.* **1997**, *339*, 426–

433; d) K. B. Simonsen, P. Bayón, R. G. Hazell, K. V. Gothelf, K. A. Jørgensen, *J. Am. Chem. Soc.* **1999**, *121*, 3845–3853; e) K. B. Jensen, M. Roberson, K. A. Jørgensen, *J. Org. Chem.* **2000**, *65*, 9080–9084; f) K. B. Simonsen, K. A. Jørgensen, Q. S. Hu, L. Pu, *Chem. Commun.* **1999**, 811–812; g) D. D. Dhavale, C. Trombini, *J. Chem. Soc. Chem. Commun.* **1992**, 1268–1270.

[8] B. Dugovič, T. Wiesenganger, L. Fišera, C. Hametner, N. Prónayová, *Heterocycles* **2005**, *65*, 591–605.

[9] DFT calculations were carried out using B3LYP exchange-correlation functionals together with 6-31G* basis set implemented in software PC GAMESS version 6.5; a) M. W. Schmidt, K. K. Baldridge, J. A. Boatz, S. T. Elbert, M. S. Gordon, J. H. Jensen, S. Koseki, N. Matsunaga, K. A. Nguyen, S. J. Su, T. L. Windus, M. Dupuis, J. A. Montgomery, *J. Comput. Chem.* **1993**, *14*, 1347–1363; b) A. A. Granovsky, PC GAMESS version 6.5, http://classic.chem.msu.su/gran/gamess/index.html.

[10] L. R. Domingo, M. J. Aurell, P. Perez, R. Contreras, *Tetrahedron* **2002**, *58*, 4417–4423.

[11] a) P. Perez, L. R. Domingo, M. Jose Aurell, R. Contreras, *Tetrahedron* **2003**, *59*, 3117–3125; b) R. Herrera, A. Nagarajan, M. A. Morales, F. Mendez, H. A. Jimenez-Vazquez, L. G. Zepeda, J. Tamariz, *J. Org. Chem.* **2001**, *66*, 1252–1263; c) L. R. Domingo, M. Arnó, P. Merino, T. Tejero, *Eur. J. Org. Chem.* **2006**, 3464–3472; d) L. R. Domingo, *Eur. J. Org. Chem.* **2000**, 2265–2272; e) L. R. Domingo, W. Benchouk, S. M. Mekelleche, *Tetrahedron* **2007**, *63*, 4464–4471.

[12] a) P. Geerlings, F. De Proft, W. Langenaeker, *Chem. Rev.* **2003**, *103*, 1793–1873; b) D. H. Ess, G. O. Jones, K. N. Houk, *Adv. Synth. Catal.* **2006**, *348*, 2337–2361.

[13] K. N. Houk, M. N. Paddon-Row, N. G. Rondan, Y. D. Wu, F. K. Brown, D. C. Spellmeyer, J. T. Metz, Y. Li, R. J. Loncharich, *Science* **1986**, *231*, 1108–1117.

[14] a) A. Dondoni, S. Franco, F. Junquera, F. L. Merchán, P. Merino, T. Tejero, V. Bertolasi, *Chem. Eur. J.* **1995**, *1*, 505–520; b) F. Degiorgis, M. Lombardo, C. Trombini, *Tetrahedron* **1997**, *53*, 11721–11730.

[15] a) P. DeShong, M. Dicken, J. M. Leginus, R. R. Whittle, *J. Am. Chem. Soc.* **1984**, *106*, 5598–5602; b) P. Merino, J. A. Mates, J. Revuelta, T. Tejero, U. Chiacchio, G. Romeo, D. Iannazzo, R. Romeo, *Tetrahedron: Asymmetry* **2002**, *13*, 173–190.

[16] For a recent application of α-methylene-β-amino acid derivatives see: a) R. Galeazzi, G. Martelli, M. Orena, S. Rinaldi, P. Sabatino, *Tetrahedron* **2005**, *61*, 5465–5473; b) D. Balan, H. Adolfsson, *Tetrahedron Lett.* **2004**, *45*, 3089–3092; c) V. Declerck, P. Ribiere, J. Martinez, F. Lamaty, *J. Org. Chem.* **2004**, *69*, 8372–8381; d) H.-Y. Chen, L. N. Patkar, S.-H. Ueng, C.-C. Lin, A. S.-Y. Lee, *Synlett* **2005**, 2035–2038; e) J. Barluenga, B. Baragana, J. M. Concellón, *J. Org. Chem.* **1999**, *64*, 2843–2846.

[17] For recent advances on the aza-Morita–Baylis–Hillman reaction see: a) K. Matsui, S. Takizawa, H. Sasai, *J. Am. Chem. Soc.* **2005**, *127*, 3680–3681; b) D. Balan, H. Adolfsson, *J. Org. Chem.* **2001**, *66*, 6498–6501; c) M. Shi, L.-H. Chen, *Chem. Commun.* **2003**, 1310–1311; d) M. Shi, Y.-M. Xu, Y.-L. Shi, *Chem. Eur. J.* **2005**, *11*, 1794–1802; e) G. Masson, C. Housseman, J. Zhu, *Angew. Chem.* **2007**, *119*, 4698–4712; *Angew. Chem. Int. Ed.* **2007**, *46*, 4614–4628.

[18] For alternatives towards aza-Morita–Baylis–Hillman products see: a) Y. Génisson, C. Massardier, I. Gautier-Luneau, A. E. Greene, *J. Chem. Soc. Perkin Trans. 1* **1996**, 2869–2872; b) D. Bierbaum, D. Seebach, *Aust. J. Chem.* **2004**, *57*, 859–863; c) W. Adam, H.-G. Degen, O. Krebs, C. R. Saha-Möller, *J. Am. Chem. Soc.* **2002**, *124*, 12938–12939; d) T. Akiyama, K. Daidouji, K. Fuchibe, *Org. Lett.* **2003**, *5*, 3691–3693; e) M. A. Loreto, A. Migliorini, P. A. Tardella, *J. Org. Chem.* **2006**, *71*, 2163–2166.

[19] a) K. B. G. Torssell, *Nitrile Oxides, Nitrones, and Nitronates*, VCH Publishers, New York, **1988**; b) I. Blanáriková-Hlobilová, Z. Kopaničáková, L. Fišera, M. K. Cyrański, P. Salanski, J. Jurczak, N. Prónayová, *Tetrahedron* **2003**, *59*, 3333–3339; c) J. Kubáň, A. Kolarovič, L. Fišera, V. Jäger, O. Humpa, N. Prónayová, *Synlett* **2001**, 1866–1868.

[20] a) S.-I. Murahashi, Y. Kodera, T. Hosomi, *Tetrahedron Lett.* **1988**, *29*, 5949–5952; b) P. Bayón, P. March, M. Figueredo, J. Font, *Tetrahedron* **1998**, *54*, 15691–15700; c) C. Chevrier, A. Defoin, *Synthesis* **2003**, 1221–1224; d) F. Machetti, F. M. Cordero, F. De Sarlo, A. Brandi, *Tetrahedron* **2001**, *57*, 4995–4998.

[21] For discussion of the possible mechanism see: a) R. P. Rebman, N. H. Cromwell, *Tetrahedron Lett.* **1965**, *6*, 4833–4836; b) N. H. Cromwell, R. P. Rebman, *J. Org. Chem.* **1967**, *32*, 3830–3833; c) M. C. Eagen, N. H. Cromwell, *J. Org. Chem.* **1974**, *39*, 3863–3866.

[22] Reaction conditions were not optimized. There was no complete conversion of isoxazolidines **4a** and **4c**, respectively. Under these conditions 14% of **4a** and 42% of **4c** were recovered.

[23] A. Dondoni, S. Franco, F. Junquera, F. Merchan, P. Merino, T. Tejero, *Synth. Commun.* **1994**, *24*, 2537–2550.

[24] a) W. Reppe, *Justus Liebigs Ann. Chem.* **1955**, *596*, 1–158; b) F. J. Weiberth, S. S. Hall, *J. Org. Chem.* **1985**, *50*, 5308–5314.

[25] C. D. Beard, K. Baum, *J. Org. Chem.* **1974**, *39*, 3875–3877.

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