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Asymmetric Synthesis of α,α-Disubstituted Amino Acids by Cycloaddition of (*E*)-Ketonitrones with Vinyl Ethers

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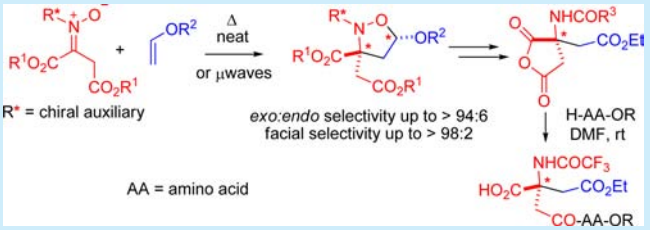
Supporting Information

ABSTRACT: Original acyclic (*E*)-α,α-dialkylketonitrones bearing a chiral auxiliary on their nitrogen atom were synthesized and successfully employed for the asymmetric synthesis of α,α-disubstituted amino acids using regio- and stereocontrolled 1,3-dipolar cycloaddition reactions with vinyl ethers. *N*-Glycosyl chiral auxiliaries were found to provide excellent *exo*- and π-facial stereocontrol. The obtained enantiopure cycloadducts were selectively transformed into functional α,α-disubstituted amino acids and related β-peptides through the highly regioselective opening of an intermediate quaternary anhydride.

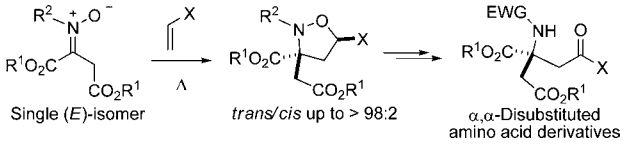


α,α-Disubstituted amino acids (DAA, quaternary amino acids) are highly valuable building blocks for the synthesis of peptidomimetics. Their limited conformational freedom induces specific restrictions in the secondary structure of oligomers in which they have been introduced.[1] However, the practical methods for their asymmetric synthesis remain limited.[2]

Recently, original ketonitrones bearing an ester function α to the C═N bond were prepared and found to exhibit an exclusive (*E*)-configuration in solution.[3,4] Interestingly, these stereochemically defined ketonitrones undergo 1,3-dipolar cycloadditions (1,3-DC)[5] with various dipolarophiles under thermal conditions, yielding *trans*-isoxazolidines in high yields when opposed to vinyl ethers. The resulting isoxazolidines bearing a quaternary stereogenic center α to a nitrogen atom could be successfully transformed into α,α-disubstituted amino acid derivatives (Scheme 1).[6]

As enantioselective methods for cycloadditions involving α-carboxy nitrones and vinyl ethers are still unavailable[5b,7] or poorly efficient,[8] we postulated that the diastereoselective 1,3-DC reaction involving "aspartic" ketonitrones equipped with a chiral auxiliary at the nitrogen atom would be a robust method to access enantiopure 5-alkoxyisoxazolidines. In a previous

Scheme 1. 1,3-Dipolar Cycloaddition Approach to α,α-Disubstituted Amino Acid Derivatives



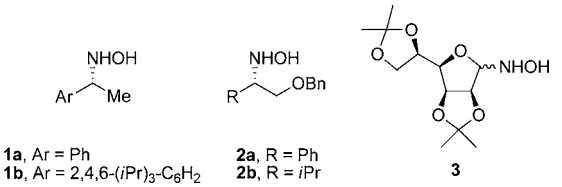


Figure 1. Hydroxylamines used as chiral auxiliaries for 1,3-DC involving ketonitrones.

communication, we have reported the preparation of ketonitrones from the α-methylbenzylamine-derived auxiliary *ent*-**1a** (Figure 1) and their thermal 1,3-DC reactions with vinyl ethers. The latter proved highly *exo*-selective, but the facial selectivity was very modest (dr ≈ 70:30).[3] In the present work, other *N*-hydroxylamines[9] have been screened as auxiliaries to evaluate their steering power in 1,3-DC reactions.

Hydroxylamines **1a**,**b** and **2a**,**b** were easily prepared from the corresponding primary amines.[10] (*R*)-*N*-Hydroxy-1-(2,4,6-triisopropylphenyl)ethylamine (**1b**) was first considered, as this auxiliary had already proved superior to its α-methylbenzylamine analogue in our hands.[11] We also considered chiral auxiliaries from the chiral pool, such as amino acid derivatives **2a**[12] and **2b**,[13] and the mannose-derived chiral auxiliary **3** (Figure 1). The latter, introduced by Vasella in the 1970s,[14] has recently gained new interest, particularly with the contributions from the groups of Carreira,[15] Skrydstrup,[16] and Bode.[17]

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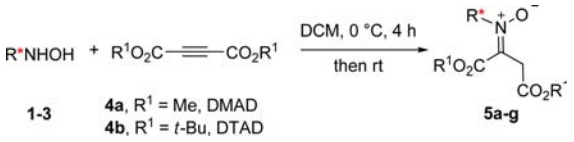
Ketonitrones **5a–g** were synthesized in high yields by condensation of dialkyl acetylene dicarboxylates **4a** (DMAD) or **4b** (DTAD) with chiral *N*-hydroxylamines **1–3** (Table 1).[3,18]

Table 1. Synthesis of Chiral Nitrones 5a–g



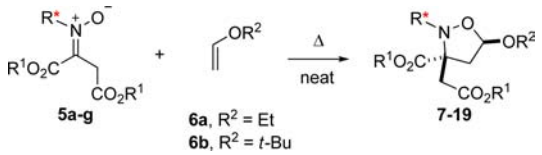
entry	R*NHOH	R^1	time at rt	nitrone	yield[a] (%)
1	**1b**	Me	2 h	**5a**	89
2	**2a**	Me	–	**5b**	92
3	**2a**	*t*-Bu	4 days	**5c**	93
4	**2b**	Me	26 h	**5d**	61
5	**2b**	*t*-Bu	5 days	**5e**	92
6	**3**	Me	4 days	**5f**	qt[b]
7	**3**	*t*-Bu	7 days	**5g**	81

[a]Isolated yield after chromatography. [b]Crude nitrone was obtained quantitatively but was unstable upon chromatography on silica gel.

Slow addition of acetylene dicarboxylates at 0 °C was essential to obtain nitrones in good yields.[19] The use of dichloromethane as solvent instead of methanol allowed direct isolation of clean products that could be used without purification by chromatography. Interestingly, nitrones **5a** and **5d** are crystalline solids, and their (*E*)-configuration was confirmed by X-ray analysis.[20]

With chiral ketonitrones **5a–g** in hand, we investigated their cycloaddition reactions with two representative vinyl ethers, **6a** (R^2 = Et) and **6b** (R^2 = *t*-Bu). By heating solvent-free mixtures of nitrones **5a–g** and vinyl ethers **6a,b** in a sealed tube, the expected cycloadducts were obtained with complete regiocontrol and excellent *exo* stereoselectivities. As a consequence, the major *trans* cycloadducts were produced in high yields, with various degrees of facial selectivities (Table 2).[21] As nitrone **5a** was found to be thermally unstable, the reaction of **5a** with **6b** was performed at 50 °C (Table 2, entry 1). Under these conditions, isoxazolidines **7** were isolated in 78% yield, as a mixture of diastereomers (*trans*/*cis* = 88:12, facial selectivity: 84:16). Nitrones **5b** and **5c**, bearing a phenylglycinol-derived chiral auxiliary, were next used in cycloaddition reaction with ethyl vinyl ether and *tert*-butyl vinyl ether (Table 2, entries 2–5). Again, the reactions occurred with complete regiocontrol and excellent to complete (in case of nitrone **5c**) *exo*-selectivity (Table 2, entries 4–5). The facial selectivity (dr ≈ 65:35) was found to be similar but no better than that observed with the 1-phenylethanamine-derived auxiliary **1a**.[3] Nitrones **5d** and **5e**, exhibiting a valinol-derived chiral auxiliary at the nitrogen atom, were found to be less reactive toward dipolarophiles **6a** and **6b**. Heating at 80 °C for more than one week was required for complete conversion of the starting materials to isoxazolidines **12–15** (Table 2, entries 6–9). With this bulky substituent on the nitrogen atom of nitrones, the facial selectivity was significantly improved (90:10 < dr < 94:6) when compared to the benzylic chiral auxiliaries. Finally, the most satisfying results were obtained with nitrones **5f** and **5g**, equipped with Vasella's chiral auxiliary (Table 2, entries 11–16). In these cases, cycloaddition was complete in 3 days at 80 °C. Cycloadducts **16–19** were formed quantitatively, again with good *exo*-selectivities (89:11 < *trans*/*cis* < 94:6) and this time with excellent facial selectivities (≥ 98:2 for nitrone **5g**). Interestingly, the cycloaddition of nitrone

Table 2. Diastereoselective Cycloaddition of Nitrones 5 with Vinyl Ethers 6



entry	nitrone	R^2	temp (°C), time[a]	cycloadducts	yield[b] (%)	*trans*/*cis*[c]	dr[c] (*trans*)
1	**5a**	*t*-Bu	50, 3 d	**7**	78	88:12	84:16
2[d]	**5b**	Et	80, 3 d	**8**	76	93:7	68:32
3[d]	**5b**	*t*-Bu	80, 3 d	**9**	72	95:5	70:30
4	**5c**	Et	80, 3 d	**10**	80	>98:2	65:35
5	**5c**	*t*-Bu	80, 3 d	**11**	72	>98:2	65:35
6	**5d**	Et	80, 21 d	**12**	93	98:2	94:6
7	**5d**	*t*-Bu	80, 13 d	**13**	83	91:9	90:10
8	**5e**	Et	80, 12 d	**14**	77	89:11	93:7
9	**5e**	*t*-Bu	80, 14 d	**15**	70	95:5	92:8
10[e,f]	**5e**	*t*-Bu	140, 4 h	**15**	qt[g]	86:14	83:17
11	**5f**	Et	80, 3 d	**16**	qt[h]	91:9	87:13
12	**5f**	*t*-Bu	80, 3 d	**17**	qt[h]	94:6	91:9
13	**5g**	Et	80, 3 d	**18**	qt[h,i]	89:11	>98:2
14[e]	**5g**	Et	100, 1 h	**18**	qt[h,i]	89:11	>98:2
15	**5g**	*t*-Bu	80, 3 d	**19**	qt[h]	94:6	98:2
16[e]	**5g**	*t*-Bu	100, 1 h	**19**	qt[h]	93:7	98:2

[a]Temperature (°C), reaction time in days (d) or hours (h). [b]Isolated yield after chromatography. [c]Determined by integration of typical signals on the NMR spectrum of the crude reaction products; see the Supporting Information. [d]Under microwave irradiation (200 W, 100 °C, 2 h) the starting materials were recovered. [e]Microwave irradiation, 200 W. [f]Under microwave irradiation (200 W, 100 °C, 1 h) only 10% nitrone **5e** was converted into the corresponding cycloadducts. [g]Quantitative conversion; the cycloadducts were not purified by chromatography on silica gel. [h]Quantitative conversion; the cycloadducts partially decomposed upon chromatography on silica gel. [i]The major diastereomer **18a** could be isolated by crystallization in EtOH in 51–58% yield.

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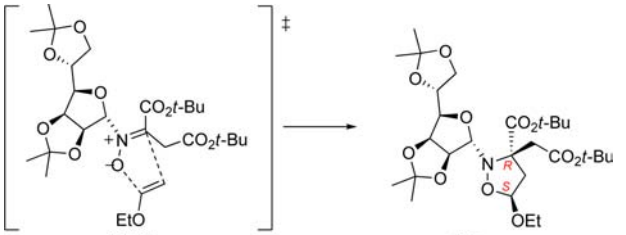
5g with vinyl ethers **6a,b** could be strongly accelerated by microwave irradiation without alteration of regio- and diastereocontrol (Table 2, entries 14 and 16). However, such acceleration of the cycloaddition reaction by microwave irradiation could not be extended favorably to the reaction of nitrones **5b** and **5e** with vinyl ethers (Table 2, entries 2−3, note *d*; entry 10, note *f*), and increasing the temperature of reaction to 140 °C (MW irradiation) resulted in lower diastereoselectivities (entries 9 and 10).

The high levels of *exo* and facial selectivities observed in the cycloaddition of ketonitrones **5f,g** with vinyl ethers are outstanding compared to those reported for 1,3-DC reactions involving other acyclic nitrones.[7] Only a few examples of such high levels of stereoinduction in 1,3-DC by *N*-glycosyl chiral auxiliaries have been reported in the aldonitrone series.[14a,22f]

Satisfyingly, the major cycloadduct **18a** could be isolated as a pure single isomer by simple crystallization from ethanol. X-ray diffraction analysis proved its 3*R*,5*S* configuration and confirmed an *exo* approach of the dipolarophile by the *Si* face of the *O*-*endo*-arranged (*E*)-ketonitrone **5g** (Scheme 2).[14d]

Scheme 2. Diastereofacial Approach of the Dipolarophiles toward the Chiral (*E*)-Ketonitrone 5f

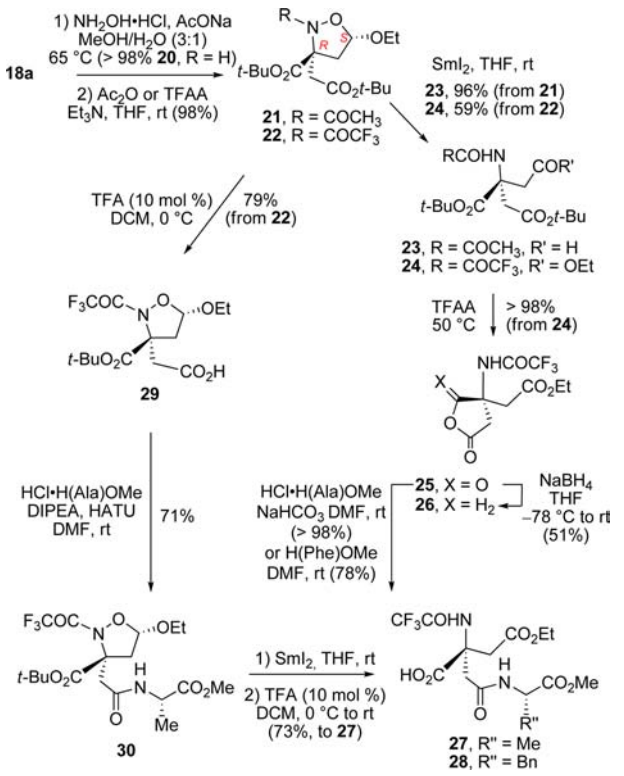


Based on NMR analysis,[21] we assume that the other cycloadditions described herein follow the same stereochemical course (*exo* approach, *trans*-cycloadducts formed preferentially). As the facial selectivity induced by chiral auxiliaries **1a,b** and **2a,b** relies on 1,3 allylic strain-induced privileged conformation of the corresponding nitrones,[7] it can be proposed that the major diastereoisomer obtained from those exhibits a 3*S*,5*R* configuration in adducts **7**−**15** (approach of the dipolarophile from the *Re* face of the nitrone).

The mannosyl chiral auxiliary was smoothly removed from cycloadduct **18a** by treatment with hydroxylamine,[15,23] providing the enantiopure isoxazolidine **20** in quantitative yield, with recovery of the auxiliary **3** (73%) that could be recycled (Scheme 3). After *N*-acetylation or *N*-trifluoroacetylation, the isoxazolidines **21** and **22** were, respectively, converted to the *β*-amino aldehyde **23** and *β*-amino ethyl ester **24** by SmI_2-mediated reductive cleavage of the N−O bond.[24] The enantiopurity of aldehyde **23** (and, by consequence of all compounds in Scheme 3) was ascertained by formation of diastereomeric imines (ee > 98%, see the Supporting Information).

At this stage, to demonstrate the utility of the *α*,*α*-disubstituted amino ester **24** for peptide synthesis, differentiation of the two *tert*-butyl esters was an essential requirement. This challenge was overcome by a highly efficient conversion of **24** to the unsymmetrical cyclic anhydride **25**, followed by regioselective transformations. For instance, treatment of **25** with $NaBH_4$ in THF at low temperature[25] yielded exclusively the lactone **26**, with no trace of regioisomeric reduction.[26] In complement,

Scheme 3. Conversion of Enantiopure Cycloadduct 18a into *α*,*α*-Disubstituted *β*-Dipeptides



anhydride **25** could be regioselectively converted into *β*-dipeptides **27** and **28**, by simple treatment with alanine methyl ester or phenylalanine methyl ester, in DMF at room temperature.[27] Compound **27** could alternatively be synthesized in three steps from isoxazolidine **22**: regioselective cleavage of the most accessible *tert*-butyl ester (10% TFA in DCM, at 0 °C) yielded the crystalline mono acid **29** whose structure was confirmed by X-ray analysis.[20] Peptidic coupling of **29** with alanine methyl ester afforded **30**, and SmI_2 reduction followed by acidic cleavage of the *tert*-butyl ester yielded the dipeptide **27**, which was identical to that obtained from opening of the cyclic anhydride **25** with alanine methyl ester. The quaternary amino acids **27** and **28** are already dipeptide equivalents and are adequately equipped for further *C*- or *N*-elongation.

In conclusion, an efficient route to enantiopure functionalized quaternary amino acids (DAA) is described, based on the diastereoselective cycloaddition of *N*-mannosyl-substituted (*E*)-ketonitrones. The chiral aspartic-based ketonitrones were readily prepared from inexpensive and recoverable sugar-derived auxiliaries. It is worthy to mention that enantiomeric amino acid precursors are expected to be accessible by using *N*-D-erythrosyl,[22f] *N*-D-ribosyl,[14a,22b] or *N*-D-gulosyl[17c−e,22a] nitrones, which have shown complementary facial selectivities in other 1,3-dipolar cycloadditions. The obtained *α*,*α*-disubstituted isoxazolidines provide access to enantiopure tetrafunctional DAA derivatives and were used for the synthesis of *β*-dipeptides containing "superaspartic" units. Further work for their incorporation in complex peptides is underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Characterization data, full experimental procedures, copies of ^1H and ^{13}C NMR spectra of all new compounds, and crystallo-

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graphic data for compounds **5a**, **5d**, **18a**, and **29** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(20) See the Supporting Information for crystallographic data.

(21) See the Supporting Information for identification and quantification of diastereomers.

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(24) The chemodivergent reduction of *N*-acetyl- vs *N*-(trifluoroacetyl) isoxazolidines by SmI_2 was discovered during our previous work on isoxazolidine ring opening; see ref 6.

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(26) NMR analysis of the crude reaction extract showed unambiguously the presence of a single product. However, the lactone **26** was isolated in only 51% yield after chromatography on silica gel.

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