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Lewis acid stereocontrolled additions of a silyl ketene acetal to 2,3-di-*O*-isopropylidene-D-glyceraldehyde nitrones. Synthesis of L-isoxazolidinyl nucleosides

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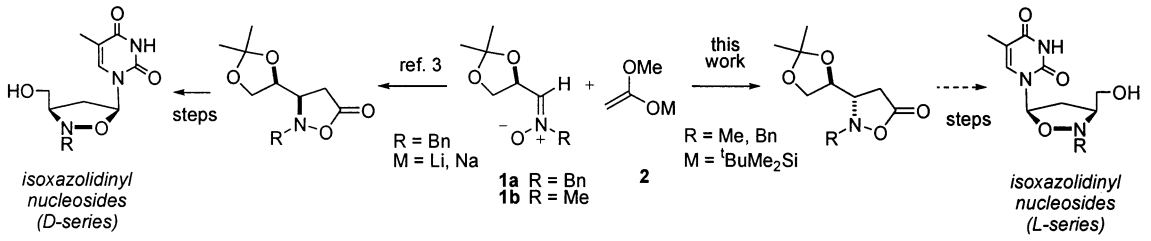
Abstract

The reaction of *O*-methyl-*O*-*tert*-butyldimethylsilyl ketene acetal with *N*-benzyl and *N*-methyl-2,3-*O*-isopropylidene-D-glyceraldehyde nitrones in the presence of boron trifluoride etherate afforded the corresponding isoxazolidin-5-ones in excellent yields and *anti*-selectivities. The obtained compounds were used as key intermediates for the synthesis of isoxazolidinyl nucleosides of the L-series. © 2000 Elsevier Science Ltd. All rights reserved.

The Lewis acid-promoted additions of various organometallic reagents to chiral nitrones are now well-established as powerful synthetic methods because they offer mild reaction conditions and high stereocontrol.[1] The key factor for the successful diastereoface differentiation, which we described some years ago, is the appropriate choice of the Lewis acid. Whereas $ZnBr_2$-promoted additions give rise to *syn*-adducts, Et_2AlCl-promoted reactions lead to *anti*-isomers preferentially.[2] Recently, we described the addition of both lithium and sodium enolates to *N*-benzyl-2,3-*O*-isopropylidene-D-glyceraldehyde nitrone (BIGN, **1a**) and applied it successfully to the efficient synthesis of novel isoxazolidine nucleosides[3] of biological importance.[4]



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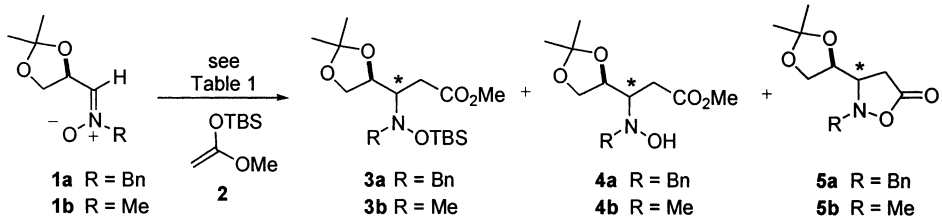
A major drawback is, however, that the Lewis acid employed to induce an *anti*-selectivity (Et_2AlCl) also reacts with the enolate thus considerably lowering the yield of the reaction.[3]

In light of our synthetic interest in novel nucleoside analogues, we sought a practical methodology for the construction of chiral isoxazolidin-5-ones with *anti*-selectivity (and then L-isoxazolidinyl nucleosides) from α-alkoxy nitrones. In this context we have recently described an alternative approach to L-isoxazolidinyl nucleosides based on the 1,3-dipolar cycloaddition reaction between **1a** and vinyl acetate.[5] The synthesis of L-isoxazolidinyl nucleosides had also been reported by Zhao et al.[6] Now, we wish to report that $BF_3{\cdot}Et_2O$ is able to induce a highly *anti*-stereoselective addition to **1**, thus achieving stereodivergency in the metal ketene acetal additions to α-alkoxy nitrones[7] and enantiodivergency in the synthesis of isoxazolidinyl nucleosides.

We examined the addition of *O-tert*-butyldimethylsilyl-*O*-methyl ketene acetal **2** to nitrones **1** in the presence of Lewis acids (Scheme 1). The results summarized in Table 1 display a marked contrast with those observed by Kita et al.[8] with ZnI_2 as a Lewis acid. These authors observed that whereas the addition of silyl ketene acetal **2** to **1a** took place with a good *syn*-selectivity,



Scheme 1.

Table 1
Stereoselective addition of ketene acetal **2** to nitrones **1** via Scheme 1[a]

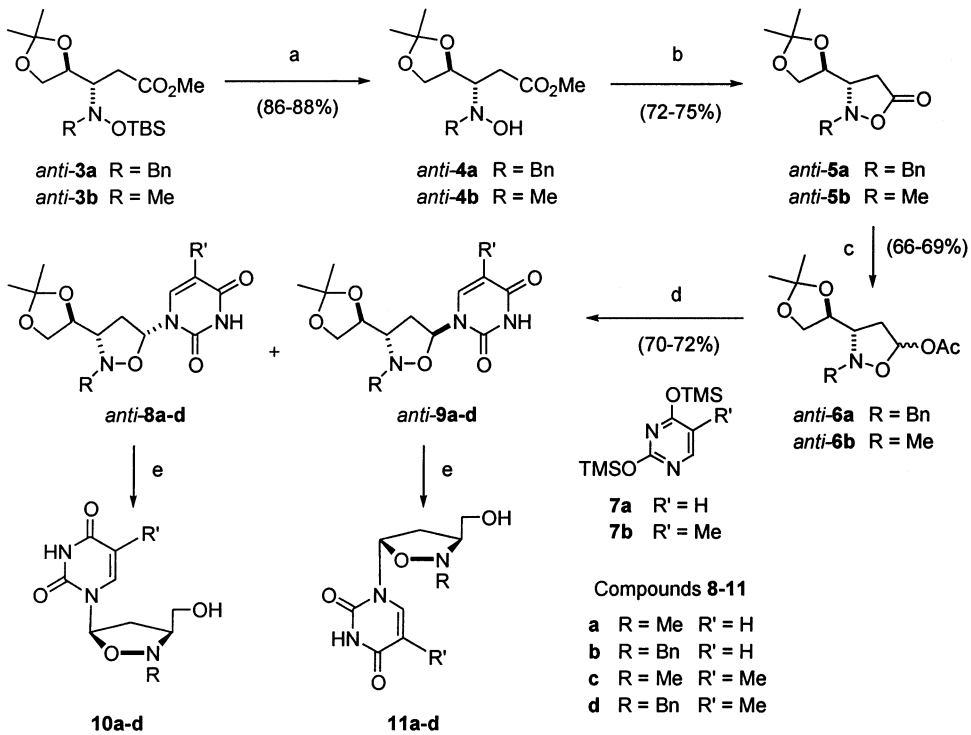
Entry	Nitrone	Conditions	Additive (equiv.)	**3**:**4**:**5**[b]	*syn*:*anti*[c]	Yield (%)[d]
1	**1a**	CH_2Cl_2, 1 h	TBSOTf (1.0)	100:0:0	77:23	91
2	**1a**	THF, 1 h	TBSOTf (1.0)	100:0:0	70:30	94
3	**1a**	Et_2O, 12 h	Et_2AlCl (1.0)	10:90:0	30:70	70
4	**1a**	CH_2Cl_2, 48 h	$BF_3{\cdot}Et_2O$ (0.1)	100:0:0	9:91	12
5	**1a**	CH_2Cl_2, 30 min	$BF_3{\cdot}Et_2O$ (1.0)	22:33:45	7:93	91
6	**1a**	CH_3CN, 30 min	$BF_3{\cdot}Et_2O$ (1.0)	17:33:50	10:90	78
7	**1a**	THF, 30 min	$BF_3{\cdot}Et_2O$ (1.0)	25:25:50	10:90	90
8	**1a**	CH_2Cl_2, 30 min	$BF_3{\cdot}Et_2O$ (2.0)	0:25:75	7:93	93
9	**1a**	CH_2Cl_2, 30 min	$BF_3{\cdot}Et_2O$ (4.0)	0:40:60	8:92	42
10	**1b**	CH_2Cl_2, 1 h	TBSOTf (1.0)	100:0:0	75:25	87
11	**1b**	Et_2O, 12 h	Et_2AlCl (1.0)	0:0:100	22:78	81
12	**1b**	THF, 30 min	$BF_3{\cdot}Et_2O$ (1.0)	0:0:100	12:88	85
13	**1b**	CH_2Cl_2, 30 min	$BF_3{\cdot}Et_2O$ (1.0)	10:0:90	7:93	92
14	**1b**	CH_2Cl_2, 30 min	$BF_3{\cdot}Et_2O$ (2.0)	0:0:100	<5:95	90

[a] All reactions were carried out at −80°C using an excess (3.0 equiv.) of enolate.
[b] Determined by NMR analysis of the crude reaction mixture.
[c] Measured over compound **5** after desilylation and cyclization.
[d] Calculated as the sum of the isolated yields of the diastereomeric mixtures of **3**, **4**, and **5**.

a near 1:1 mixture of diastereomers was obtained when an *O-tert*-butyl ketene acetal was used as a nucleophile.[9]

In our experiments, the addition of **2** to nitrones **1** led to a mixture of silylated hydroxylamines **3**, free hydroxylamines **4** (only observed with nitrone **1a**) and isoxazolidinones[10] **5**, depending on both the nature and stoichiometry of the Lewis acid.

When nitrone **1a** was treated with TBSOTf and then with ketene acetal **2**, compound **3a** was obtained in good yield and *syn*-selectivity (entries 1 and 2). The same result was observed with nitrone **1b** (entry 10). However, when Et_2AlCl was used as a pre-complexing agent of **1a**, a mixture of hydroxylamines **3a** and **4a** was obtained and the *anti*-isomers became predominant with acceptable diastereoselectivities (entry 3). In the case of nitrone **1b** the *anti*-selectivity was also observed but only cyclized compound **5b** was obtained (entry 11). The use of $BF_3{\cdot}Et_2O$ in a catalytic amount afforded **3a** exclusively with a good level of *anti*-selectivity (entry 4). Unfortunately, the yield of the reaction was only 12%, presumably due to the necessity of stoichiometric amounts of additive; actually, nitrone **1** was recovered in nearly 80% yield. In fact, 1.0 equiv. of $BF_3{\cdot}Et_2O$ increased the yield of the reaction to 91%, without a substantial lost of selectivity (entry 5). Under these conditions, a 2:3:4 mixture of compounds **3a**, **4a** and **5a** was obtained. This result was only slightly affected by a change of solvent (entries 6 and 7). An excess of 2.0 equiv. of $BF_3{\cdot}Et_2O$ enriched the mixture of obtained compounds into the cyclic one **5a**, no silylated hydroxylamine **3a** being observed (entry 8). Also, in this case both the yield and *anti*-selectivity showed high values. In an attempt to obtain only the isoxazolidin-5-one **5a**, we



Scheme 2. Reagents and conditions: (a) HF, Py, 0°C, 30 min; (b) NaOMe, MeOH, rt, 4 h; (c) DIBAH, CH_2Cl_2, −80°C, 1 h, then Ac_2O, Py, 0°C, 30 min; (d) **7a** (or **7b**), TMSOTf, CH_2Cl_2; (e) *p*-TosOH (cat.), MeOH, then $NaIO_4$, MeOH (aq.), then $NaBH_4$, MeOH, 0°C, 45 min

checked the addition in the presence of 4.0 equiv. of $BF_3{\cdot}Et_2O$ (entry 9). However, under these conditions the yield of the reaction dropped considerably.[11] The reversal of the stereoselectivity by the use of $BF_3{\cdot}Et_2O$ was also for nitrone **1b** (entries 12–14), the best result found, being obtained when 2.0 equiv. of additive were used (entry 14).

The diastereoselectivities of the processes were measured over compounds **5** after desilylation of **3** (HF, Py) and cyclization of **4** (NaOMe, MeOH)[12] as shown in Scheme 2. The stereochemistry of isoxazolidinones **5a** was assigned by X-ray crystallographic analysis of a single crystal of the major isomer *anti*-**5a**.[13] The structure of compounds **5b** was deduced by comparison of physical and spectroscopic data[14] with those described in the literature[9] for *syn*-**5b**.

With respect to the synthetic utility of compounds *anti*-**5**, they were converted into the corresponding 5-acetoxy isoxazolidines *anti*-**6** by reduction (DIBAH, CH_2Cl_2) and subsequent acetylation (Ac_2O, Py). These key intermediates were further transformed into L-isoxazolidinyl nucleosides **10a–d** and **11a–d** (Scheme 2)[14] according to the Vörbruggen conditions[10,15] and following our previously described protocol,[5] which had been successfully applied for the synthesis of isoxazolidinyl thymidines **10d** and **11d**.

In summary, the results presented here represent the first evidence that silyl ketene acetals can be added to α-alkoxy nitrones with complete stereocontrol starting from the same substrate. The application of this methodology has served for providing access to L-isoxazolidinyl nucleosides in higher yields than those reported previously.[5,6] In addition, both D- and L-series are accessible starting from D-glyceraldehyde nitrones as the only chiral sources.

Acknowledgements

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References

1. For an account, see: (a) Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *Synlett* **2000**, 442–454. For reviews, see: (b) Lombardo, M.; Trombini, C. *Synthesis* **2000**, 759–774. (c) Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. In *Recent Research and Development in Synthetic Organic Chemistry*; Pandalai, S. G., Ed.; Transworld Research Network: Trivandrum, India, 1998; Vol. 1, pp. 1091–1121. (d) Merino, P.; Tejero, T. *Molecules* **1999**, *4*, 165–175.
2. For some leading references, see: (a) Merino, P.; Castillo, E.; Franco, S.; Merchan, F. L.; Tejero, T. *J. Org. Chem.* **1998**, *63*, 2371–2374. (b) Merino, P.; Castillo, E.; Franco, S.; Merchan, F. L.; Tejero, T. *Tetrahedron: Asymmetry* **1998**, *9*, 1759–1769. (c) Merino, P.; Castillo, E.; Franco, S.; Merchan, F. L.; Tejero, T. *Tetrahedron* **1998**, *54*, 12301–12322. (d) Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *Tetrahedron: Asymmetry* **1997**, *8*, 3489–3496.
3. Merino, P.; Franco, S.; Garces, N.; Merchan, F. L.; Tejero, T. *Chem. Commun.* **1998**, 493+.
4. For a review, see: Pan, S.; Amankulor, N. M.; Zhao, K. *Tetrahedron* **1998**, *54*, 6587–6604.
5. Merino, P.; del Alamo, E. M.; Franco, S.; Merchan, F. L.; Simon, A.; Tejero, T. *Tetrahedron*: *Asymmetry* **2000**, *11*, 1543–1554.
6. Xiang, Y.; Gong, Y.; Zhao, K. *Tetrahedron Lett.* **1996**, *47*, 4877–4880.
7. For other additions of ketene acetals to nitrones, see: (a) Ohtake, H.; Imada, Y.; Murahashi, S.-I. *J. Org. Chem.* **1999**, *64*, 3790–3791. (b) Jost, S.; Gimbert, Y.; Greene, A. E.; Fotiadu, F. *J. Org. Chem.* **1997**, *62*, 6672–6677. (c) Camiletti, C.; Dhavale, D. D.; Donati, F.; Trombini, C. *Tetrahedron Lett.* **1995**, *36*, 7293–7296.
8. Kita, Y.; Tamura, O.; Itoh, F.; Kishino, H.; Miki, T.; Kohno, M.; Tamura, Y. *Chem. Commun.* **1988**, 761–763.

9. The same authors reported, however, that when a bulky group (CH(Me)Ph or $CHPh_2$) was attached to the nitrone, nitrogen *anti*-selectivity was observed, particularly in the case of nitrones derived from 4-deoxy-L-erythrose. See: Kita, Y.; Itoh, F.; Tamura, O.; Ke, Y. Y.; Tamura, Y. *Tetrahedron Lett*. **1987**, *28*, 1431–1434.
10. There is a precedent for such an intramolecular cyclization in the presence of a Lewis acid. See: Xiang, Y.; Gi, H.-J.; Niu, D.; Schinazi, R. F.; Zhao, K. *J. Org. Chem*. **1997**, *62*, 7430–7434.
11. This is presumably due to occurrence of dioxolane ring-opening promoted by an excess of Lewis acid. See: DeGiorgis, F.; Lombardo, M.; Trombini, C. *Tetrahedron* **1997**, *53*, 11721–11730.
12. The global process consisting of desilylation and cyclization can also be carried out over crude mixtures of compounds **3**, **4** and **5** in order to obtain, in a one-flask process, isoxazolidinones **5**.
13. The authors have deposited atomic coordinates for the structure of *anti*-**5a** with the Cambridge Crystallographic Data Centre (deposition number: CCDC 149829). Data for *syn*-**5a** had also been deposited previously (see Ref. 3).
14. Selected data (solvent for optical rotations: $CHCl_3$) for *anti*-**5a**: $[\alpha]_D^{20}=-36$ (*c* 1.13); *anti*-**5b**: $[\alpha]_D^{20}=-95$ (*c* 1.11); **10a**: $[\alpha]_D^{20}=-14$ (*c* 0.28); **10b**: $[\alpha]_D^{20}=-33.4$ (*c* 0.40); **10c**: $[\alpha]_D^{20}=-11$ (*c* 0.8); **10d**: $[\alpha]_D^{20}=-6$ (*c* 1.10); Ref. 5: $[\alpha]_D^{20}=-7$ (*c* 1.10); **11a**: $[\alpha]_D^{20}=-43$ (*c* 0.31); **11b**: $[\alpha]_D^{20}=-98$ (*c* 0.29); **11c**: $[\alpha]_D^{20}=-23$ (*c* 0.16); **11d**: $[\alpha]_D^{20}=-38$ (*c* 0.89); Ref. 5: $[\alpha]_D^{20}=-36$ (*c* 1.11). Full experimental details and characterization, data are available from the authors upon request.
15. Vörbruggen, H.; Kvolikiewicz, K.; Bennua, B. *Chem. Ber*. **1981**, *114*, 1234–1255.