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NOREPHEDRINE DERIVED 2-METHOXY OXAZOLIDINES AS CHIRAL FORMYL CATION EQUIVALENTS#

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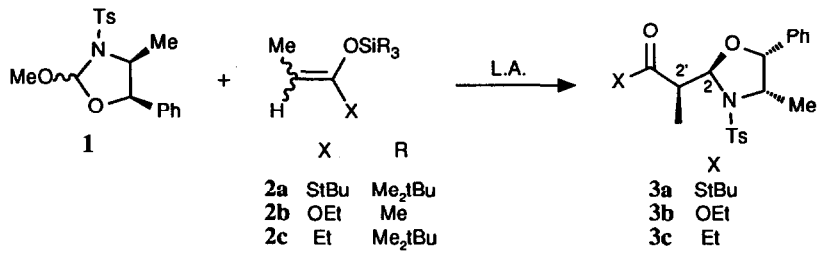
Abstract. *Lewis acid catalyzed reaction of silylenolethers with* ***1*** *followed by a straightforward nondestructive removal of the chiral auxiliary affords the corresponding aldehydes in good e.e. Compound* ***1*** *represents the first effective chiral synthetic equivalent of formyl cation.*

Formyl cation synthetic equivalents have wide applications in synthetic organic chemistry. Although a number of such synthons have been reported,[1-4] to the best of our knowledge there are no examples of reagents which are designed to add preferentially to one enantioface of π-nucleophiles.[5,6] In this paper we describe the synthesis and reactivity of orthoamide **1**, the first formyl cation equivalent that can add with a high degree of enantioface differentiation to silylketeneacetals and silylenolethers.

Scheme I



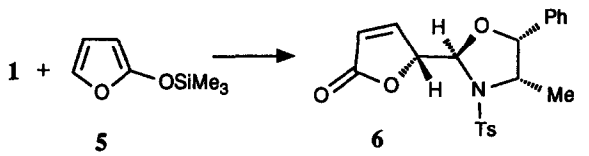
	X	R
2a	StBu	Me_2tBu
2b	OEt	Me
2c	Et	Me_2tBu

	X
3a	StBu
3b	OEt
3c	Et

The cyclic orthoamide **1**[7] was synthesized as a 1:1 mixture of C-2 epimers by condensing trimethylorthoformate and (1R,2S)-N-tosyl-norephedrine[8] in refluxing benzene and in the presence of pyridinium tosylate as a catalyst. Upon treating this mixture with 2 molar equivalents of silylketenethiolacetal **2a** in the presence of $SnCl_4$ (Scheme I), only two isomers were formed in a 96:4 diastereomeric ratio (Table I, Entry 1). The configuration of the major isomer **3a**[7] was determined by X-ray diffraction[9] and found to be (2R, 2'R), as indicated in Scheme I. Such very effective discrimination between the enantiofaces of the nucleophile seems to be largely independent of both the silylketeneacetal configuration (Table I, Entries 2-4) and of the Lewis acid used to promote the addition (Table I, Entries 1, 2 and 5). As it is often the case for acid catalyzed additions to ester silylketeneacetals, reaction with **2b** (Table I, Entries 6, 7) was found to be rather unselective. The most abundant isomer formed in this process has the same configuration as the one isolated upon reaction of **1** with

2a. This was proved by reducing both to the same alcohol **7**[7] (see Scheme III). On the contrary, 2-trimethylsilyl-oxyfuran **5** reacted with **1** (Scheme II) to give a major compound **6**[7] in diastereomeric excess up to 88% (Table I, Entry 12).

Scheme II



Also in this case the product configuration was proved to be (2R, 2'R) by X-ray crystallography.[9] A diastereomeric excess up to 92% (Table I, Entry 10) was obtained with diethylketone dimethyl-*t*-butylsilylenol-ether **2c** (Table I, Entries 8-10). The configuration of the major isomer has not yet been determined, and it is assumed to be (2R, 2'R) by analogy with the results described above.

Table I. Addition of silylethers to **1**.[a]

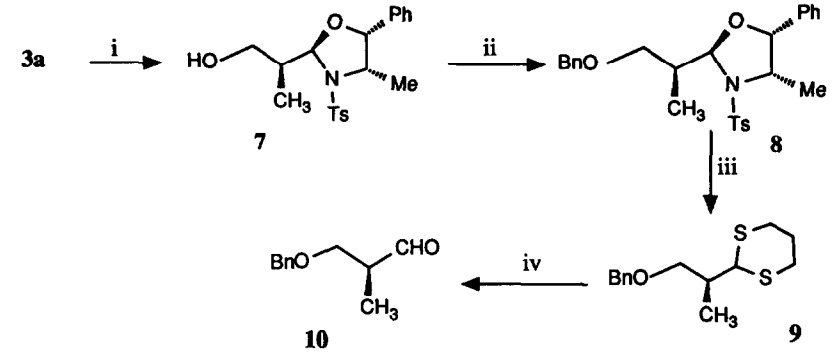
Entry	Nuc	Lewis acid[b]	Diast.exc.(%)[c]	yield(%)[d]
1	Z-**2a**	$SnCl_4$	92	85(83)
2	Z-**2a**	BF_3OEt_2	92	90
3	E-**2a**	BF_3OEt_2	92	90
4	**2a** 2:1E/Z	BF_3OEt_2	92	92(91)
5	E-**2a**	Me_3SiOTf[e]	84	87(85)
6	**2b**[f]	$SnCl_4$	--	--[g]
7	**2b**[f]	BF_3OEt_2	50	97(95)
8	Z-**2c**	Me_3SiOTf	78	67
9	Z-**2c**	$TiCl_4$	88	92
10	Z-**2c**	BF_3OEt_2	92	56
11	**5**	$tBuMe_2SiOTf$	74	78(75)
12	**5**	$tBuMe_2SiOTf$[h]	88	95(90)

a.Unless otherwise stated, reactions were performed by adding the Lewis acid to a CH_2Cl_2 1:2 solution of **1** and **2** at -78°C. Reaction is usually over within 2h at this temperature. The main byproduct is O-formyl-N-tosyl-norephedrine **4**, from hydrolysis of **1**. b.The following amounts of Lewis acid were used: $SnCl_4$, 1.4eq; BF_3OEt_2, 2.0eq; $TiCl_4$, 1.4eq; Me_3SiOTf and $tBuMe_2SiOTf$, 0.25eq. c.Determined by ^1H- and ^{13}C-NMR spectroscopy. d.Yield as determined by NMR on the crude reaction mixtures;isolated yields in brackets. e.Reaction performed at -20°C. f.**2b** was used as a 85:15 E/Z mixture. g.Only formate **4** was isolated (see note a). h.Reaction performed at -100°C.

Removal of the chiral auxiliary completed the formylation process. So, for instance, **3a** was transformed in

82% total yield into the corresponding benzylether **8**[7] (i.LAH; ii.$PhCH_2Br$, Bu_4NOH, Scheme III) from which optically pure (1R, 2S)-N-tosyl norephedrine was smoothly released upon treatment with 1,3-propanedithiol in the presence of BF_3Et_2O. Dithiane **9**[7] was then submitted to hydrolysis ($CaCO_3$, MeI, H_2O) and aldehyde **10** was isolated in 92% e.e., as measured by $[\alpha]_D$.[10]

Scheme III *Removal of the auxiliary*



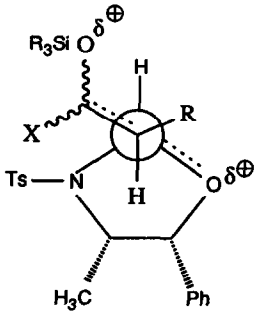
i. $LiAlH_4$ (95%)

ii. $PhCH_2Br$ / NaOH/Bu_4NHSO_4 (86%)

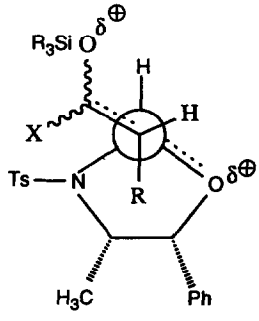
iii. $HS(CH_2)_3SH$ / $BF_3.Et_2O$ / CH_2Cl_2 (73%)

iv. $CaCO_3$/MeI/H_2O/acetone (65%)

Assuming that the reaction takes place through an oxazolinium ion,[11] the observed stereoselection can be explained by acyclic extented transition structures. In this hypothesis, addition of the silylenol ether to the less hindered side of the oxazolidine ion [12] can occur through transition structure **A** or **B**.[13] Structure **A**, which gives rise to the 2' (R) epimer, should be lower in energy, because it minimizes steric interactions between the silylether substituent and the cycle. Work is in progress to clarify the mechanistic aspects of this reaction as well as to explore the synthetic scope of the method.



A



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References and Notes

(#) This work was presented in part at the *OMCOS V - Fifth IUPAC Symposium on OrganoMetallic Chemistry Directed Towards Organic Synthesis* 1-6 Oct. **1989**, Firenze, Italy, Communication OP-A29.

(1) Orthoformates: Pindur,U.; Müller,J.; Flo,C. and Witzel,H. *Chem.Soc.Rev.* **1987**, *16*, 75 and ref. therein; Suzuki, M.; Yanagisawa, A.; Noyori, R. *Tetrahedron Lett.* **1982**, 3545; Takazawa, O.; Kogami, K.; Hayashi, K. *Bull.Chem.Soc.Jap.* **1984**, *57*, 1876; Mock, W.L.; Tsou, H-R *J.Org.Chem.* **1981**, *46*, 2557.

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(3) 2-Ethoxy-1,3-dithiolane: Hatanaka,K.; Tanimoto,S.; Sugimoto,T. and Okano,M. *Tetrahedron Lett.*, **1981**, 3243.

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(5) Chiral formyl cation equivalents derived from ephedrine and tartaric acid were studied by G.Boche and J.Bigalke and found to be poorly reactive toward nucleophiles: Bigalke, J. *Inaugural Dissertation zur Erlangung del Grades eines Doktors der Naturwissenschaften*, Marburg/Lahn **1988**. We thank Prof. Boche for sending us a copy of this work.

(6) A few chiral equivalents of acyl cations have appeared in the literature: Nagao,Y.; Hagiwara,Y.; Tohjo,T.; Hasegawa,Y.; Ochiai,M. and Shizo,M. *J.Org.Chem.* **1988**, 53, 5983; Kunisch,F.; Hobert,K. and Welzel.P.; *Tetrahedron Lett.* **1985**, 5433; Basile, T.; Longobardo, L.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *OMCOS V-Fifth IUPAC Symposium on OrganoMetallic Chemistry directed towards Organic Synthesis*, 1-6 Oct. **1989**, Firenze, Italy, Communication OP-A23

(7) All new compunds have been fully characterized by the usual spectroscopic means.

(8) Bernardi, A.; Cardani, S.; Pilati, T.; Poli, G.; Scolastico, C.; Villa, R. *J.Org.Chem.* **1988**, *53*, 1600.

(9) Details of the X-ray structure determination will be given in a full paper.

(10) $[\alpha]_D$=+27.3°(c=1.14, $CHCl_3$); lit.value $[\alpha]_D$=+28.4°(c=1.56, $CHCl_3$): Roush, W.R.; Adam, M.A.; Peseckis, S.M. *Tetrahedron Lett.* **1983**, 1377; Paterson, I.; Lister, M.A. *Tetrahedron Lett.* **1988**, 585.

(11) Tomalia, D.A.; Paige, J.N. *J.Org.Chem.* **1973**, *38*, 422

(12) It may be noted that in the X-ray structures of both **3a** and **6** the tosyl group is oriented in the same hemispace occupied by the norephedrine phenyl and methyl groups. If this is the case also in the transition state, the N protecting group can contribute to hindering the approach of the nucleophile from this side of the ring.

(13) We have no direct evidence that the oxazolidine ion is mainly located on the oxygen rather than on the nitrogen atom. On the other hand, the N lone pair should be of low basicity because of the inductive effect of the tosyl group. The formation of formylester **4** (as opposed to the corresponding amide) upon hydrolysis of the cation is supportive of this view (see ref. 11).

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