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Chiral 2-Lithio-1,3-Dioxolanes and -2-Lithiooxazolidines: New Formyl Anion Equivalents.

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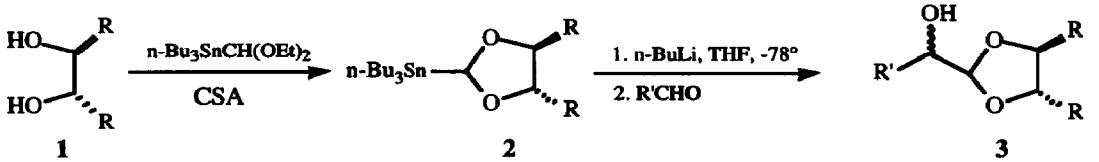
Abstract: The preparation of enantiomerically pure 2-lithio-1,3-dioxolanes and 2-lithiooxazolidines and their use as formyl anion equivalents in addition reactions to aldehydes are described.

Chiral variants of formyl anion equivalents[1] have been realized using almost exclusively dithio- and hemithioacetal-derived reagents[2] in which either a sulfoxide group or stereogenic carbon centers close to the reactive nucleophilic site are exploited as the source of chirality. A totally different approach, developed by Davies, was based on an optically active α-alkoxyacyl iron complex.[3] The unmasking of the sulfur based functions is often the most difficult step of the synthetic sequence and, furthermore, almost all methods for the cleavage of the thioacetal and thioacetal S-oxide groups do not allow the recovery of the chiral auxiliary.
The ease of acetal hydrolysis to aldehydes as well as the potential of acetals as precursors of other functionalities, prompted us to explore the use of chiral 2-lithio-1,3-dioxolanes as chiral formyl anion equivalents in reactions with aldehydes.
The preparation of achiral (dialkoxymethyl)lithium reagents, 2-lithio-1,3-dioxolanes and 2-lithio-1,3-dioxanes from the corresponding stannyl derivatives as well as their reactions with electrophiles are well documented.[4] Thus we prepared a series of optically pure 2-stannyl-1,3-dioxolanes **2** by the acid catalyzed transacetalisation between (diethoxymethyl)tri-*n*-butylstannane[4] and C_2 symmetric 1,2-diols **1**. Reaction with *n*-butyllithium at -78° followed by addition of an aldehyde gave the expected α-hydroxyacetals **3** in yields close to 90%.

Scheme 1



1 **2** **3**

a R = Me
b R = Cyclohexyl
c R = Ph
d R = $CH(Me)_2OMe$
e R = $CH(Me)_2OBn$

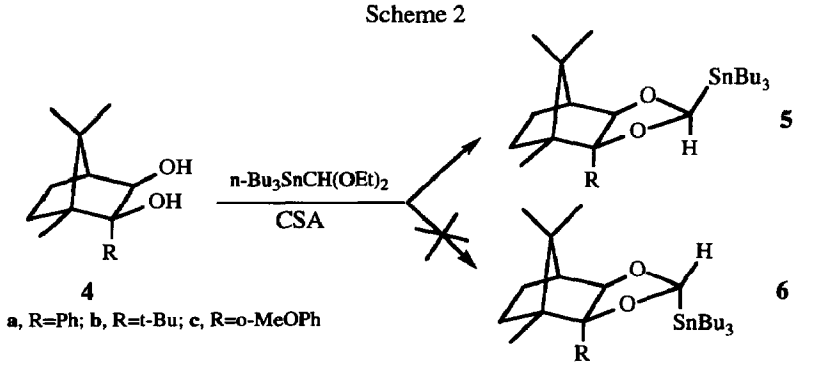
Table 1

entry	compound	yield%	compound	yield% (diast.ratio)
1	**2a**	70	**3a** (R'=Ph)	90 (55:45)
2	**2b**	73	**3b** (R'=Ph)	88 (70:30)
3	**2c**	90	**3c** (R'=Ph)	-
4	**2d**	65	**3d** (R'=Ph)	87 (75:25)
5	**2e**	70	**3e** (R'=Ph)	85 (75:25)
6			**3a** (R'=i-Pr)	93 (60:40)
7			**3d** (R'=i-Pr)	89 (70:30)

The diastereomeric ratios illustrated in Table 1 clearly show that the level of asymmetric induction essentially depend on the size of the R substituents placed on the dioxolane ring. A small group such as a methyl had no effect on stereodifferentiation. A more sterically demanding cycloehexyl group or a quaternary carbon center greatly improved diastereoselection. However, modest diastereomeric excesses were obtained in every case and no substantial difference between the reactions of aromatic or aliphatic aldehydes was apparent. A possible explanation of the low stereochemical bias inherent in these systems may derive from the conformational flexibility[5] of the dioxolane ring. In the reactive conformation, the ring substituents responsible for chiral discrimination are evidently placed in pseudo-equatorial positions and consequently are too remote from the reactive site, so that a strong interaction with the R' group of the incoming aldehyde is precluded. On the basis of these considerations we planned the synthesis of more rigid dioxolanes by means of the fusion with a canphane skeleton bearing a bulky substituent in a pseudo-axial position. This would be a good working model only if the transacetalisation reaction could lead to a stannylacetal **6** with the tin atom in an "endo" position, that is pointing toward the bulky R substituent. This configuration should be maintained in the lithium derivative, as it is known that a net retention of configuration is usually observed in tin-lithium exchange reactions.[6]

Transacetalisation of canphandiols **4a-c** [7] gave 2stannyl-1,3-dioxolanes as single diastereomers in excellent yields.However, n.O.e. difference experiments showed unequivocally that the undesired isomers **5** were formed in all cases.

Scheme 2



4

a, R=Ph; **b**, R=t-Bu; **c**, R=o-MeOPh

These isomers **6** were shown by molecular mechanics calculations to be more stable than **5** by *ca* 2 Kcal/mol.[8]

As expected, transmetalation of these unbiased systems with *n*-butyllithium and direct addition of benzaldehyde gave adducts in good yields but with poor diastereoselection.

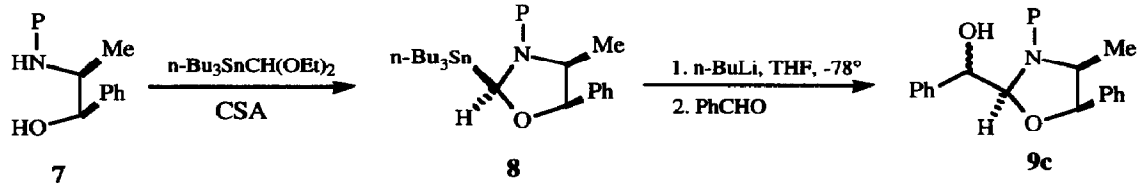
In addition to these drawbacks, we found that all the above α-hydroxy dioxolanes, protected as methyl or benzyl ethers, were extremely resistant to any attempt of acid hydrolysis to α-alkoxy aldehydes. This severe limitation persuaded us that further investigation on diol-based reagents would have been fruitless.

In order to overcome the difficulties encountered in the unmasking of the dioxolane funtion, we thought that the use of a more easily hydrolizable oxazolidine ring[9] would be advantageous. Moreover, even if the addition reactions of chiral 2-lithiooxazolidines to aldeheydes were to prove unselective, the resulting 2-hydroxyalkyl oxazolidines could be oxidized to the corresponding acyl derivatives whose subsequent reduction should afford the sought 2-hydroxyalkyloxazolidines with high diastereoselection. This prediction was based on recent findings by Poli and Scolastico,[10] who reported one case of highly selective reduction of a norephedrine-derived 2-acetyloxazolidine. It seemed to us plausible the assumption that similar high diatereoselection would be extensible to the general class of 2-acyl oxazolidines.

Thus we prepared a series of hitherto unknown 2-stannyloxazolidines **8** by the acid catalyzed exchange reaction of N-protected (1R,2S)-norephedrine with (diethoxymethyl)tri-*n*-butylstannane. The choice of the protecting group was crucial for the ensuing tin-lithium exchange reaction. The N-tosyl derivative **8a** resisted all attempts at transmetalation by treatment with either *n*-butyl or *sec*-butyl lithium whereas the reaction of the 2-stannyl N-carbobenzyloxy oxazolidine **8b** with lithium bases produced an intractable mixture.

Finally, the N-*t*-butoxycarbonyl derivative **8c** smoothly reacted at -78° with *n*-butyllithium giving the metalated adduct[11] which in turn afforded in 90% yield the expected 2-hydroxialkyloxazolidine **9c** by addition of benzaldehyde. The only shortcoming of the sequence is the modest yield of the transacetalization step. A mixture of two diasteroisomers was formed and the major component **8c** was isolated by chromatography in 35-40% yield. An nOe difference experiment on the major isomer showed that the tributylstannyl moiety is cis to the methyl and phenyl substituents, thus assigning the S configuration to the newly created stereocenter. The addition reaction with benzaldehyde gave a mixture of only two diasteroisomers **9c** with poor diastereoselection. Oxidation of the mixture with pyridinium dichromate gave a single ketone, demonstrating that the two isomers were epimers at the hydroxy bearing carbon. This was confirmed by nOe experiments on both isolated isomers **9c**. These results show that also in the case of 2-stannyl-oxazolidines the tin-lithium exchange reaction occurs with complete retention of configuration.

Scheme 3



7

a, P=Ts; **b**, P=Cbz; **c**, P=t-Boc

8

Yield % **a** 50; **b** 48; **c** 40

9c

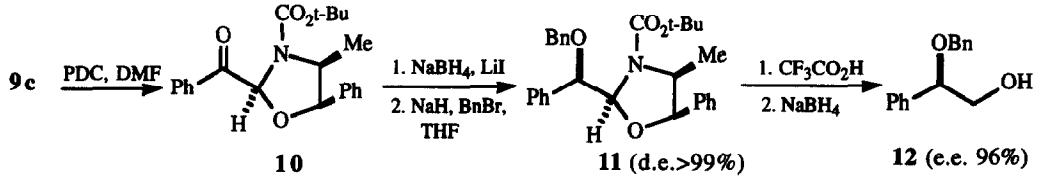
Y=90%

Oxidation of the diastereomeric mixture with pyridinium dichromate gave, as mentioned above, a single ketone **10** whose reduction with $NaBH_4$ afforded two diasteromeric alcohols in a satisfactory 15:1 ratio. Addition of LiI enhanced the diastereoselection of the reduction step. The disatereomeric ratio, determined by HPLC, was higher than 100:1 (80% overall yield for the oxidation-reduction sequence).

The hydroxy group was then protected as a benzyl ether in essentially quantitative yield and the *t*-Boc group was removed by brief treatment with trifluoroacetic acid. Treatment of the crude deprotected oxazolidine

with THF/H_2O effected the hydrolysis to the aldehyde which was reduced in situ with $NaBH_4$ to afford 2-benzyloxy-2-phenyl ethanol **12** in 70% overall yield. The sign of optical rotation indicated an R absolute configuration.[12] The enantiomeric excess was determined by the Mosher method[13] and the 96% e.e. value demonstrated that only marginal racemisation occurred during the unmasking procedure.

Scheme 4



10 **11** (d.e.>99%) **12** (e.e. 96%)

In conclusion we have demonstrated that optically pure 2-stannyloxazolidines can be used as efficient chiral formyl anion equivalents. We are currently investigating the potential of different β-amino alcohol chiral auxiliaries in order to improve yield and diasteroselection of the transacetalisazion step and canphor based reagents proved very promising in this respect.

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