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Camphor-Derived 2-Stannyl-N-Boc-1,3-Oxazolidine: a New Chiral Formylanion Equivalent for the Asymmetric Synthesis of 1,2-Diols

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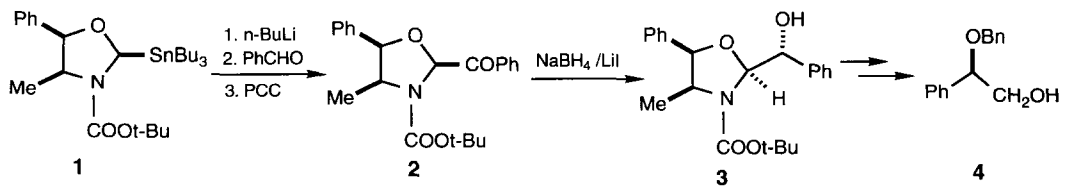
Abstract : *Optically pure 2-tributylstannyl-N-Boc-1,3-oxazolidine* ***6****, prepared from the camphor-derived aminoalcohol* ***5****, was converted to diastereomerically pure 2-acyl derivatives* ***8*** *in three steps. Reaction of these ketones with Grignard reagents at -78°C proceeded with high stereoselectivity affording tertiary carbinols which gave 1,2-diols with >96% ee after hydrolysis and reduction of the intermediate α-hydroxy aldehydes. A new deblocking procedure of the t-Boc group is also described.*

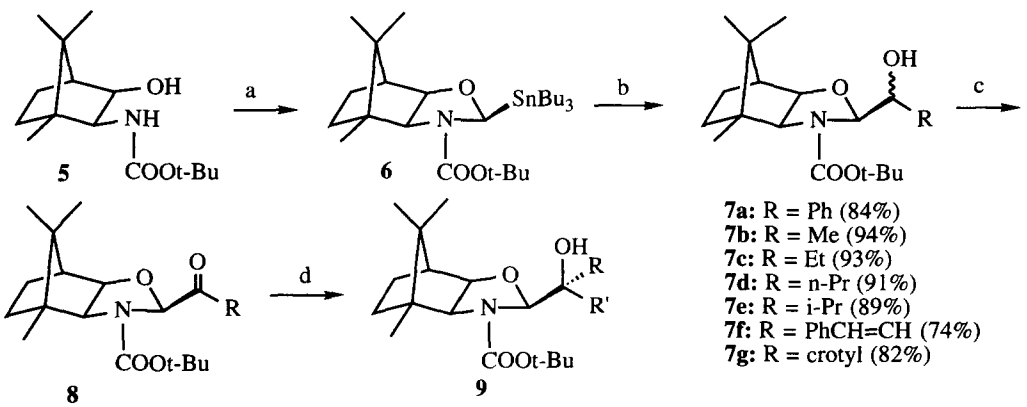
The asymmetric nucleophilic formylation is a powerful tool which allows the synthesis of optically active α-hydroxy carbonyl compounds, starting from achiral aldehydes. A number of chiral formyl anion equivalents[1] utilizing dithio and hemithioacetal-derived reagents have been reported and of these Eliel's oxathianes[2] have been widely used. However, successful asymmetric synthesis based on these reagents is not only dependent on efficient chirality transfer but also on the possibility of easy recovery of the chiral auxiliary in the final step of the synthetic sequence. In order to expand the generality of this methodology, the issue of deprotection of the masked carbonyl group is crucial. Recently we have shown that 2-tributylstannyl-N-Boc-1,3-oxazolidine **1** can be used as a valuable chiral formylanion equivalent.[3] Transmetallation of this reagent with n-butyllithium at -78°C in THF afforded the expected 2-lithiooxazolidine which was reacted with benzaldehyde to give a mixture of only two diastereoisomeric alcohols, epimers at the hydroxyl bearing carbon. The usefulness of **1** as an effective chiral formylanion was shown by the highly stereoselective reduction of 2-benzoyl-1,3-oxazolidine **2**, obtained by oxidation of the above mixture of secondary alcohols, to give **3** as a single stereoisomer. This in turn was benzylated and converted to the monoprotected diol **4** by a two-step sequence involving deprotection of the masking oxazolidine followed by $NaBH_4$ reduction of the resulting α–alkoxy aldehyde. The very low level of racemisation occuring during the unmasking procedure clearly demonstrates the potential of N-Boc-oxazolidines as efficient chiral formylanions (Scheme1).



Scheme 1

These results were successively confirmed by Agami et al.[4] who reported a new synthetic approach to diastereoisomerically pure ephedrine derived N-Boc-2-acyloxazolidines from phenylglyoxal and ethyl glyoxylate. Addition of Grignard reagents to N-Boc-2-acyloxazolidines was proved to occur with complete stereoselectivity affording diastereomerically pure tertiary carbinols.

The only shortcoming of our method is the low diastereoselectivity and consequently the poor yields associated with the preparation of stannane **1.** In order to circumvent this problem we decided to investigate the potential of different β-amino alcohols as chiral auxiliaries. Reminiscent of our previous experience with the transacetalisation reaction of 1,2-camphandiol with (diethoxymethyl)tributylstannane[5] which we have shown to give diastereomerically pure 2-stannylacetals[3] in good yields, the structurally related camphor-derived aminoalcohol **5**[6] seemed to us as ideal for our purpose. Transacetalisation of the aminoalcohol **5** with (diethoxymethyl)tributylstannane led to stannyloxazolidine **6** as a single isomer in 70% yield. The configurational assignment of the newly created stereocenter as S (exo-isomer) rests securely on its n.O.e. difference spectrum showing that all the protons of the oxazolidine ring are placed on the same face. As expected, oxazolidine **6** underwent rapid Sn/Li exchange by treatment with n-butyllithium at -78°C affording the corresponding 2-lithium derivative which in turn reacted with a variety of aldehydes. Secondary alcohols **7a-g** were thus obtained in 80-90% yield as diastereomeric mixtures of only two stereoisomers. Oxidation of these alcohols, differing from the configuration of the newly formed stereocenter, with Dess-Martin periodinane[7] afforded acyloxazolidines **8** in a very good yield (90-98%) (Scheme 2). ^1H and ^{13}C NMR spectra showed that oxazolidines **8** were stereochemically homogeneous compounds and the assignment of an S absolute configuration to C_2 of the oxazolidine ring was made possible by n.O.e. experiments.



a) $Bu_3SnCH(OEt)_2$, CSA (30 mole %), benzene, reflux, 15 min. b) n-Butyllithium (1.3 eq.), THF, -78°C; after 1min. RCHO (1.5 eq.), -78°C, 1h. c) 1.3 eq. periodinane, CH_2Cl_2, rt, 1h. d) 3 eq. R'MgX, THF-Et_2O, -78°C, 1h.

Scheme 2

The data reported in table 1 clearly demonstrates the general applicability of this procedure, since aliphatic, aromatic and α,β-unsaturated 2-acyloxazolidines were easily synthesized from their corresponding aldehydes.

Ketones **8a-g** were succesively converted into tertiary carbinols **9a-k** by addition of Grignard reagents (3 eq.) in THF/Et_2O at -78°C. As expected, from the observation of ^1H and ^{13}C NMR spectra of the crude product mixtures, only one isomer was detected in all cases tested. If R and R' group are interchanged as components of the aldehyde and the Grignard reagents the product with opposite configuration at the

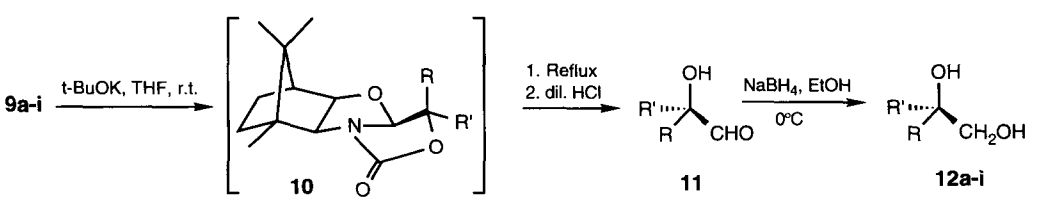
hydroxyl bearing carbon is obtained with similar efficiency in terms of yield and stereoselection. Ultimately this could lead to the obtention of both enantiomers of α-hydroxy aldehydes through the assistance of the same chiral auxiliary. Two remarkable features shared by all proton NMR spectra of compounds **9a-d** are the downfield shift of the hydroxy proton (δ 8.0-8.2 ppm) and the upfield shift of the camphor geminal methyl protruding towards the oxazolidine nucleus (δ -0.1-0.1 ppm). Moreover, the latter anomaly was not observed in the corresponding epimeric compounds **9e,f,i**. This data is in accordance with the presence of a strong intramolecular hydrogen bond between the hydroxy proton and the t-Boc carbonyl oxygen[8] thus locking the R and R' substituents in fixed positions. Such a rigid molecular arrangement should force the phenyl appendage of isomers **9a-d** to face one geminal methyl group thus allowing the configurational assignment of the quaternary center.

Table 1: prepared oxazolidines **8** and **9**

Substrate	ketones	alcohols	R	R'	overall yield	Diast. ratio[b]
7a	**8a**	**9a**	Ph	Me	96%	>98:2
		9b	Ph	Et	92%	>98:2
		9c	Ph	i-Pr	54%	>98:2
		9d	Ph	vinyl	90%	>98:2
7b	**8b**	**9e**	Me	Ph	85%	>98:2
7c	**8c**	**9f**	Et	Ph	80%	>98:2
		9g	Et	n-Pr	93%	>98:2
7d	**8d**	**9h**	n-Pr	Et	92%	>98:2
7e	**8e**	**9i**	i-Pr	Ph	77%	>98:2
7f	**8f**	**9j**	PhCH=CH	Me	70%[a]	>98:2
7g	**8g**	**9k**	crotyl	Me	74%[a]	>98:2

a) 3 eq. MeMgI, THF/Et_2O, -78°→ 0°C, 3h. b) The ratio was determined by ^1H NMR.

Confirmation of this hypothesis has come from the comparison with literature data of the optical rotations of final diols **12a-i**,[2,4] obtained by deprotection of the chiral auxiliary. Attempts to cleave the t-Boc group by acid treatment under various conditions were unsuccessful, leading to extensive decomposition probably due to competitive dehydration reaction of the tertiary alcohol function. Recourse to a treatment with excess t-BuOK[9] in hot THF for 30 minutes followed by acidification to pH 2 and stirring for 1hour gave our target aldehydes **11** which were immediately subjected to reduction with $NaBH_4$ at 0°C in ethanol (Scheme 3 and Table 2).



Scheme 3

Table 2: Chiral glycols **12** synthesized

compd.	R	R'	$[\alpha]_D^{20}$	config.	ee, %[a]	overall yield, %[b]
12a	Ph	Me	-12.84[c]	R	>96%	100%
12b	Ph	Et	+11.03[d]	R	>96%	94%
12c	Ph	i-Pr	+16.95[e]	R	>96%	94%
12d	Ph	vinyl	+41.2[c]	R	>96%	83%
12e (*ent-12a*)	Me	Ph	+4.76[f]	S	>96%	100%
12f (*ent-12b*)	Et	Ph	-13.95[g]	S	>96%	95%
12g	Et	Pr	-5.3[h]	S	>96%	86%
12h (*ent-12g*)	Pr	Et	+5.4[h]	R	>96%	86%
12i (*ent-12c*)	i-Pr	Ph	-9.23[c]	S	>96%	95%

a) e.e. were determined by the Mosher method[10] (^{1}H NMR analysis). b) Overall, from carbinols **9**.
c) c= 1.0EtOH. d) c= 3.0 EtOH. e) c= 6.3 EtOH. f) c= 4.2 EtOH. g) c= 0.6 EtOH. h) c= 1.0 $CHCl_3$.

The mechanism of this deblocking procedure probably involves the hydrolysis of the strained oxazolidinones **10** we have isolated as stable intermediates. This procedure allowed the easy recovery of the chiral auxiliary in 85% yield.

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