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A CHIRAL REAGENT INDUCING ASYMMETRY IN ELECTROPHILIC AMINATION REACTIONS

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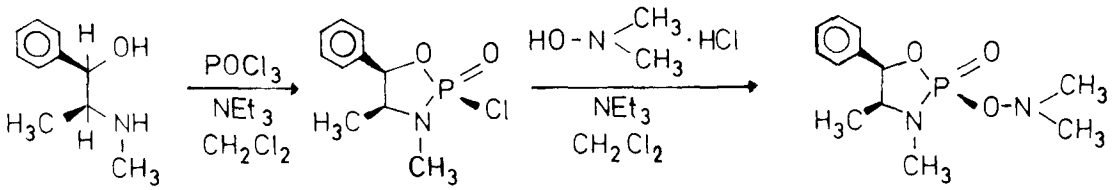
Abstract: The chiral amination reagent (-)-1 was prepared from (-)-ephedrine, configurationally determined by X-ray structure analysis and reacted with carbon nucleophiles to yield the optically active amines 4a-d with up to 44% ee.

Among the many reactions which have been developed for the preparation of chiral compounds within the last decade[1], only few deal with chiral leaving groups to induce asymmetry, as shown by recent publications[2,3]. It is especially the communication of Kjaer and Malver[3] that prompts us to disclose the synthesis, X-ray structure determination of the absolute configuration, and application of (2R,4S, 5R)-2-O-(N,N-dimethylhydroxylamino)-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one, (-)-1, for the formation of chiral amines.

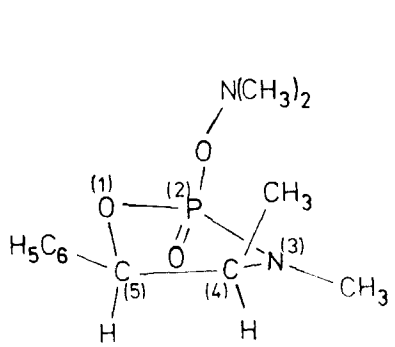
Preparation of (-)-1. When (-)-ephedrine in methylene dichloride/triethylamine was reacted with phosphorus oxychloride and subsequently with the hydrochloride of N,N-dimethylhydroxylamine ($(CH_3)_2N$-OH·HCl), (-)-1 was formed in 68% yield via (-)-2[4].



(-)-2 (-)-1

Similarly, from (+)-ephedrine, (+)-1 is easily accessible by means of this one-pot synthesis[5].

Configuration of (-)-1. Since the absolute configuration of (-)-ephedrine is known[6], it was easy to assign the absolute configuration of (-)-1 from its X-ray structure[7]. As shown by the ORTEP drawing (Fig. 1), the N,N-dimethylhydroxylamino group is on the same side of the five-membered ring as the substituents at C^4 and C^5. Thus, the transformation 2 → 1 occured under retention of configuration at the phosphorus atom.



(-)-1

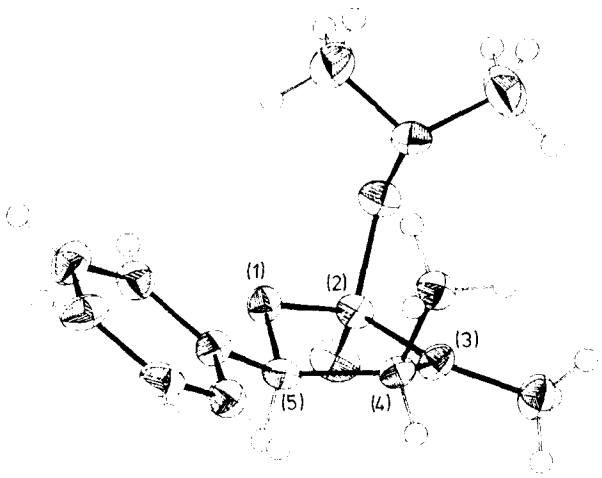
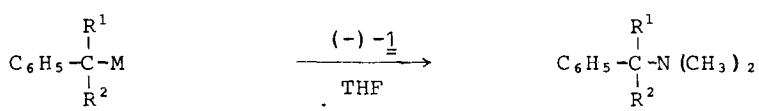


Fig. 1. ORTEP drawing and numbering of (-)-1.

Formation of chiral amines. The development of the electrophilic amination reaction within the last few years allows the introduction of amino groups with various amination reagents in all kinds of nucleophiles[8-11]. We were interested in the preparation of chiral amines by this method. Therefore, the organometallic compounds 3a-d were reacted with (-)-1 and the amount of enantiomer excess (% ee) of the products 4a-d determined by optical rotation or shift reagents. The first not yet optimized results are listed in Tab. 1.

Tab. 1. Asymmetric induction by (-)-1 in electrophilic amination reactions with 3 to give 4.



3 4

3		[°C]	amine 4	% yield	opt. yield (% ee)[a]
3a	H C6H5-C-MgCl CH3	-15	4a	63	30[b]
		-75	4a	46	24[b]
3a'	H C6H5-C-MgBr CH3	-15	4a	40	44[b]
		-75	4a	35	19[b]

3a'' [d]	$(C_6H_5-\overset{H}{\overset{\vert}{C}}-\overset{CH_3}{\vert})_3B$	-10	4a	26.5 [e]	11 [b]
3b	$C_6H_5-\overset{H}{\overset{\vert}{C}}-\overset{CO_2Et}{\vert}\ ^{\ominus}Li^{\oplus}$	-15	4b	50	23 [c]
3c	$C_6H_5-\overset{CH_3}{\overset{\vert}{C}}-\overset{CO_2Et}{\vert}\ ^{\ominus}Li^{\oplus}$	-15	4c	56	21 [c]
3d	$C_6H_5-\overset{H}{\overset{\vert}{C}}-\overset{CN}{\vert}\ ^{\ominus}Li^{\oplus}$	-15	4d	62	8 [c,f]

[a] Optical purities given as % ee (error ±5%) were determined by [b] optical rotation after gc purification and [c] with $Eu(tfc)_3$ in $CDCl_3$; [d] prepared in situ from the Grignard reagent; [e] the yield is related to three alkyl groups in 3a''; [f] presumably, the ee value does not correspond to the amount of asymmetric induction because of facile racemization of 4d during normal acid (pH 4.5)/base (pH 8) workup.

Further substrates and optically active, electrophilic amination reagents from chiral amino alcohols and diols are under investigation.

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References and Notes

1. e.g. a) J.P. Morrison, H.S. Mosher, "Asymmetric Organic Reactions", Prentice Hall, Englewood Cliffs, New Jersey, 1972; b) Y. Izumi, A. Tai, "Stereodifferentiating Reactions", Academic Press, New York, 1977; c) A.I. Meyers, Acc. Chem. Res. 11, 375 (1978); d) H.B. Kagan, J.C. Fiaud, Topics in Stereochemistry 10, 175 (1978); e) J.W. ApSimon, R.P. Seguin, Tetrahedron 35, 2797 (1979) f) P.A. Bartlett, Tetrahedron 36, 2 (1980).
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3. A. Kjaer, O. Malver, Tetrahedron Lett. 1982, 2687, reacted the amination reagent (+)-O-(α-bromocamphor-π-sulfonyl)-hydroxylamine, e.g., with methyl p-tolyl sulphide; the aminated product had an (R)-enantiomer excess of "only a few percent". Isolation of the optically pure compounds therefore was

achieved by crystallization.

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5. The following general procedure applies for the preparation of (-)-1 (and similar amination reagents) from (-)-ephedrine (and similar amino alcohols/-diols): To 0.10 mol amino alcohol/diol and 50.6 g (0.50 mol) triethylamine in 700 ml CH_2Cl_2 was added 15.3 g (0.10 mol) $POCl_3$ at -5°C. Then the reaction mixture was stirred at 10°C for 14 h. After the addition of 9.75 g (0.10 mol) $(CH_3)_2N$-OH·HCl stirring was continued at 20°C for another 24 h, the ether insoluble ammonium salt separated by filtration, and the solvent evaporated. Crystallization or column chromatography provided the analytically pure product. (-)-1: 18.5 g (68%); m.p.: 140°C (diisopropyl ether); $[\alpha]_{589}^{20}$ = -82.7; $[\alpha]_{365}^{20}$ = -276.1 (c = 2.57, $CHCl_3$).
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7. We are very grateful to Dr. W. Massa and G. Baum, Fachbereich Chemie der Universität Marburg, for the X-ray structure determination.
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