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ENANTIOSELECTIVE ALKYLATION OF ALDEHYDES VIA METALATED CHIRAL HYDRAZONES

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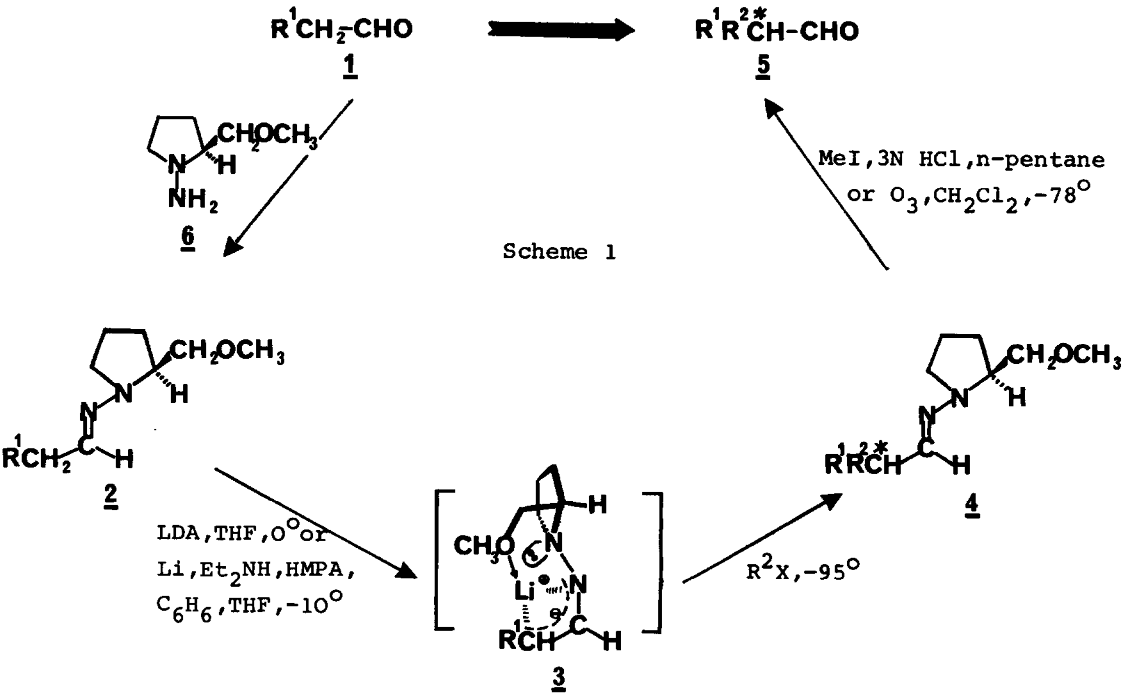
We recently reported an efficient asymmetric synthesis of α-substituted ketones by metalation and alkylation of chiral hydrazones[1]. α-chiral aldehydes 5, which are valuable as reactive chiral synthons in organic synthesis[2] and for mechanistic studies, are hard to prepare[3]. Methods using optical activation via immonium salts[4] or asymmetric hydroformylation[5] give only aldehydes of low enantiomeric purity.

We describe here the first asymmetric synthesis of α-chiral aldehydes via C-C bond formation 1→5 (scheme 1) in good chemical yields and, in some cases, high enantiomeric purity. As the chiral auxiliary we use (S)-1-amino-2-methoxymethyl-pyrrolidine 6, easily prepared in four steps (55% overall yield) from commercially available (S)-proline[1].



Scheme 1

The method involves conversion of the aldehydes 1 into the chiral hydrazones 2, metalation with lithium diisopropylamide (LDA) in THF at 0° [6] (method A) or with Li/Et_2NH/HMPA/benzene/THF at -10° [7] (method B) and alkylation at -95° to 4. The now α-substituted aldehydes 5 are regenerated by hydrolysis of the methiodides[8] of 4 in a two-phase system (3N HCl, n-pentane) or by ozonolysis (CH_2Cl_2,-78°)[9]. The ozone cleavage permits recovery of the chiral reagent 6[1]. The results of various alkylations are summerized in table 1.

The hydrazones 2 and 4 are oils, which can be purified by distillation or column chromatography[10], while the lithium compounds 3 precipitate from the reaction mixtures. As indicated in formula 3 the lithium ion is probably intramolecularly chelated to provide a conformative rigidity necessary for a high asymmetric induction[11]. Although the Cahn-Ingold-Prelog rules cause 5a to be assigned the S configuration, all aldehydes are configurationally related since the chelates 3 are preferably alkylated from the topside (from above the plane of the paper)[12].

Since the aldehydes 5 can be reduced (see footnote c in table 1) and oxidized without racemization the corresponding β-chiral alcohols and α-chiral acids are also available by this method.

Improvement and further development by variation of the chiral auxiliary as well as the carbonyl compounds and electrophiles are in progress.

(R)-2-Methyloctanal 5e. Compound 6 (2.6g, 20 mmol) is treated dropwise with n-octanal (3.12ml,20mmol) with stirring at 0°. After 2 hr the crude product is dissolved in CH_2Cl_2 and the resulting solution dried over sodium sulfate, concentrated in a rotary evaporator, and finally purified by column chromatography (silicagel, n-pentane/ether 3:1). 2, R^1= n-C_6H_{13}, is obtained in 96% yield (4.6g) as a colorless oil, $[\alpha]_D^{22}$= -103°(c=1.8, benzene). 2 (2.4g,10mmol) is metalated according to the method of Normant et al.[7](metalation time 10h), cooled to -95° and treated with a solution of methyliodide (0.68ml,11mmol) in 15 ml THF. The mixture is stirred for a further 3 hr and allowed to warm to room temperature. After hydrolysis, work up with ether yields 4, R^1= n-C_6H_{13}, R^2= CH_3, 2.3g (91%). The crude product is treated with excess methyliodide and stirred at 60° for 5 hr. The resulting salt is hydrolysed in a two-phase system (3N HCl, n-pentane) by rapid stirring for 30 min. 5e is purified by molecular distillation over glass wool (oil bath temperature 100°/3 torr).

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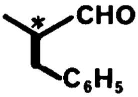
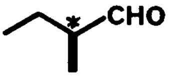
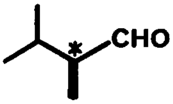
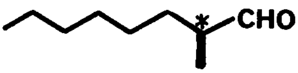
Table 1. α-Chiral aldehydes 5 prepared by asymmetric synthesis. The newly coupled C-C bonds are shown in bold print. Compounds 4 were generally converted into 5 by hydrolysis of the methiodides; 5b and 5f, however, were obtained by ozonolysis.

	aldehyde	R^2X	$[\alpha]_D^T$(c,solvent)[a]	%ee(cfg.)	% overall yield[b]
5a		$C_6H_5CH_2Br$	$+4^{20}$(1.25,acetone) c	82 (S)	62
5b		CH_3I	-20.2^{20}(2.3,acetone) -31.4^{20}(2.73,acetone)[2]	62 (R)	65
5c		CH_3I	-36.9^{20}(neat) -65.2 (neat)[14]	57 (R)	60
5d		CH_3I	-26.6^{20}(0.95,acetone) d	(R)	67
5e		CH_3I	-25.8^{20}(neat) -29.76^{25}(neat)[e]	87 (R)	61
5f		$(CH_3)_2SO_4$	-74.1^{25}(neat) -238^{25}(neat)[f]	31 (R)	80[g]

a) First value: rotation of the distilled, spectroscopically (ir, pmr) pure aldehydes. Second value: highest rotation quoted in the literature (values in degrees). - b) Obtained with metalation method B. - c) Not previously reported; 5a was reduced with $BH_3 \cdot THF$ complex to (S)-2-benzylpropanol $[\alpha]_D^{22}$= -10° (neat), 82% ee, based on $[\alpha]_D^{26}$= +12.2° (neat)[13]; determination of % ee of 5a using the chiral shift reagent tris[3-(heptafluoro-1-hydroxybutylidene)-(d)-campherato]europium(III) failed. - d) Not previously reported; by comparison with the rotation of 5b we assume that 5d is of high enantiomeric purity. - e) Calculated from the data reported in ref. 5. - f) Calculated max. rotation, the highest measured rotation reported in the literature is about 40°[15]. - g) Metalation method A was used.

References and Notes

1. D. Enders and H. Eichenauer, *Angew. Chem.* **88**, 579 (1976); *Angew. Chem. Int. Ed. Engl.* **15**, nr 9 (1976).
2. For a recently reported application see: K. Banno and T. Mukaiyama, *Chem. Lett.* 279 (1976).
3. G. Otani and S. Yamada, *Chem. Pharm. Bull.* **21**, 2112 (1973) and lit. cited therein; aldehydes of type 5 can be prepared starting from chiral precursors, e.g. alcohols [E.J. Badin and E. Pascu, *J. Amer. Chem. Soc.* **67**, 1352 (1945)], alkylhalides [D. Seebach, D. Steinmüller, and F. Demuth, *Angew. Chem.* **80**, 618 (1968); *Angew. Chem. Int. Ed. Engl.* **7**, 620 (1968)] or steroids[14].
4. H. Matsushita, M. Noguchi, M. Saburi, and S. Yoshikawa, *Bull. Chem. Soc. Jap.* **48**, 3715 (1975).
5. G. Consiglio, C. Botteghi, C. Salomon, and P. Pino, *Angew. Chem.* **85**, 663 (1973); *Angew. Chem. Int. Ed. Engl.* **12**, 669 (1973).
6. While 2, $R^1 = C_6H_5$, can be metalated quantitatively under these conditions in 2 hr, in all other cases about 25 % of starting material is recovered even after 15 hr metalation time; for the metalation of N,N-dimethylhydrazones (DMH's) see: E.J. Corey and D. Enders, *Tetrahedron Lett.* 3,11(1976); E.J. Corey, D. Enders, and M. G. Bock, *ibid.* 7 (1976).
7. T. Cuvigny, J.F. Le Borgne, M. Larchevêque, and H. Normant, *Synthesis* 237 (1976); quantitative metalation of compounds 2 is possible with prolonged metalation times (10 hr).
8. M. Avaro, J. Levisalles, and H. Rudler, *Chem. Commun.* 445 (1969).
9. R.E. Erickson, P.J. Andrulis, J.C. Collins, M.L. Lungle, and G.D. Mercer, *J. Org. Chem.* **34**, 2961 (1969).
10. The new compounds 2 and 4 give correct elemental analyses; ir, pmr, and mass spectra are in agreement with the given structures.
11. The fact that the rotations of the product aldehydes 5 are independent of the metalation method A or B used (even though in procedure B the strongly cation-solvating HMPA is present) points to a strong chelation in 3; after metalation of aldehyde-DMH's[6] and reaction with electrophiles the thermodynamically less stable Z-isomers predominate in the crude products; this indicates the ability of the amino-nitrogen to chelate in metalated hydrazones.
12. For a similar situation in chiral metalated 2-oxazolines see: A.I. Meyers, G. Knaus, K. Kamata, and M.E. Ford, *J. Amer. Chem. Soc.* **98**, 567 (1976).
13. K.B. Wiberg and T.W. Hutton, *J. Amer. Chem. Soc.* 78, 1640 (1956).
14. K. Rsuda, Y. Kishida, and R. Hayatsu, *J. Amer. Chem. Soc.* **82**, 3396 (1960).
15. C. Botteghi, G. Consiglio, and P. Pino, *Liebigs Ann. Chem.* 864 (1974).