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CHIRAL HOMOENOLATE EQUIVALENTS. I. ASYMMETRIC SYNTHESIS OF ß-SUBSTITUTED ALDEHYDES VIA METALATED CHIRAL ALLYLAMINES

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Abstract: Metalated chiral allylamines of type 2 (M = Li, K) are used as chiral homoenolate equivalents and allow after alkylation and acidic hydrolysis asymmetric C-C bond formations to ß-substituted aldehydes in enantiomeric excesses up to 67%.

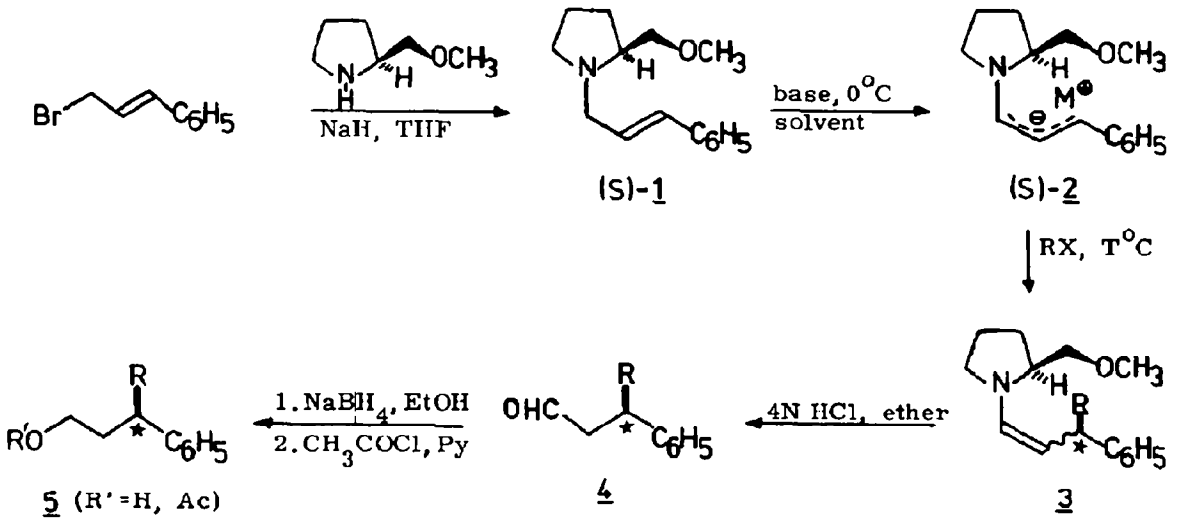
In view of the often different biological activity of enantiomers the synthesis of pharmaceuticals, food additives, pheromones, etc. of high enantiomeric purity is of considerable significance and a challenge in synthetic organic chemistry. An elegant chiral economic solution to this problem is asymmetric synthesis [1], and in this connection the development of new synthetic methods, especially for asymmetric C-C bond formation, is most important. Although several general and highly efficient methods for asymmetric C-C bond formation in α-(via alkylation) [2] and ß-position (via Michael-type addition) [3] to the carbonyl group have been described recently, an alternative method for the latter process via C-C-connective asymmetric electrophilic substitution is not available to date.

Such a process should be possible via equivalents of chiral homoenolates [4] A as for example deprotonated enamines or allylamines of type B using the highly efficient chiral inducer (S)-2-methoxymethyl-pyrrolidine [2b].

A ≡ B

We wish to describe here our preliminary results on the chiral allylamine (S)-1, easily prepared from cinnamylbromide and (S)-2-methoxymethyl-pyrrolidine [5] (80%). The allylic anion (S)-2, obtained by deprotonation of (S)-1, is alkylated with methyliodide to the enamine 3a (R = CH_3) with high diastereoselectivity. Acidic hydrolysis in a two phase system followed by a Kugelrohr distillation furnishes the pure, optically active ß-substituted aldehyde 4a. The enantiomeric purity was determined by optical rotation and nmr-shift-experiments after transformation to the corresponding alcohol 5a (R'=H) and acetate (R'=Ac) according to scheme 1 (exp. details see table 1).

scheme 1



As can be seen, the enantiomeric excess (ee) varies with the gegenion, solvent, and temperature. In THF the better solvated lithium salt gives the lower ee in comparison with the potassium salt(run 1.2). Changing the solvent from THF to the less complexing petrol ether leads to a remarkable increase of ee (run 1.2 - run 3.4). Under these conditions no dependence on the gegenion is observed. From these results the tightest ion pair is expected to give the highest asymmetric induction. Raising the temperature leads to a decrease in selectivity (run 4.5). The best result was obtained at -100°C under the conditions of run 6.

Table 1. Optimization of asymmetric induction (RX = CH_3I).

run	base	M	solvent	T[°C]	ee[%] [a]
1	t-BuLi/t-BuOK	K [b]	THF	-78	37
2	t-BuLi	Li	THF	-78	26
3	t-BuLi	Li	petrol ether	-78	63
4	t-BuLi/t-BuOK	K [b]	petrol ether	-78	64
5	t-BuLi/t-BuOK	K [b]	petrol ether	0	49
6	t-BuLi	Li	petrol ether	-100	67

a) Determined ^{1}H-nmr-spectroscopically ($CDCl_3$, peak height method) on the acetyl-signal of 5a (R'=Ac) by means of tris[3-heptafluoro-1-hydroxybutylidene)-(d)-campherato] europium (III).

b) Using the Lochmann-Schlosser-base [6] actually potassium is the gegenion [4].

Due to a side reaction during the metalation step (addition of the base to the styrene system) the chemical yield of enamine 3a in some cases was rather moderate. Since this side reaction is supressed using the Lochmann-Schlosser-base [6], for further investigations (variation of RX) we used the conditions given in table 2. As can be seen, the enantiomeric excess is almost independent on the size of the alkylating agent and with about 65% ee rather high. It drops to about 50% ee by changing from iodides to bromides. In all cases we performed double determinations from independent experiments - the reproducibility is excellent. This is not trivial, since under these conditions the reactions are heterogeneous (the K-salt (S)-2 precipitates).

Table 2. Asymmetric γ-alkylations of the deprotonated allylamine (S)-2 (conditions: M=K, petrol ether, -78°C).

	RX	3 c.y.[%][a]	c.y.[%][b]	4 b.p. [°C/torr][c]	5 $R'=H\ [\alpha]_D^{20}$ (neat) $R'=Ac\ [\alpha]_D^{20}$ (c, benzene)	ee[%][d] (Confg.)
a	CH_3I	54	50	66/0.2	-24.9° [e] -35.2° (3.36)	64;65 (R)
b	C_2H_5I	57	34	120/1	-25.9° (2.2)	65;65 (R)[f]
c	$i\text{-}C_3H_7I$	60	73	103/0.2	-10.3° -23.4° (3.67)	65; 66 (S)[f]
d	$n\text{-}C_4H_9Br$	74	89	122/0.2	-3.4° [g] -15.3° (4.37)	47;48 (R)[h]
e	$CH_2{=}CHCH_2Br$	63	49	116/0.2	-5.3° -15.4° (5.0)	50; 51 (R)[f]

a) Determined by v.p.c. (OV 101 at 100-250°C, temperature programm, 15°C/min.). - b) Yields of pure distilled 4 based on 3(not optimized). - c) Oven temperature during Kugelrohr-distillation. - d) Determined nmr-spectroscopically as indicated in table 1. - e) $[\alpha]_D^{25} = -39.0°$ (neat) [7]. - f) Assigned tentatively by comparison of the rotations observed, similar behaviour during shift-experiments, and assuming a unique reaction mechanism. - g) $[\alpha]_D^{27} = -1.45°$ (neat) 8 $\hat{=}$ ee = 17.9% (calculated by comparison with the max. rotation of 3-phenyl-heptanoic acid [3a]). - h) 42% ee based on the rotation given in footnote g).

The anion (S)-2 is formed in the "sickle"-configuration shown, as was evident from the (Z)-configuration of the product enamines 3 after non-aqueous work up ($^3J_{HH}$ = 8.8 cps). During the usual aqueous work up, however, the (E)-enamines are formed ($^3J_{HH}$ = 13.6 cps).

In summary we have shown that chiral homoenolate equivalents [9] can be used efficiently for asymmetric C-C bond formation in ß-position to the carbonyl group of aldehydes (introduction of electrophiles) and offer an attractive alternative to the recently developed asymmetric Michael-additions [3] (introduction of nucleophiles).

Further investigations on the scope and mechanism of this reaction as well as the development of other, even more efficient, chiral homoenolate equivalents [10] are in progress [11].

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References and Notes

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9) To the best of our knowledge (S)-2 is the first chiral homoenolate equivalent.

10) First results with metalated phosphoramidates as chiral homoenolate equivalents are promising, D. Enders, H. Lotter, unpublished.

11) The spectroscopic data and elementary analyses of all new compounds are in agreement with the structures given.

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