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ASYMMETRIC SYNTHESIS OF ALDEHYDES VIA ALKYLATION OF LITHIATED CHIRAL α-PHENETHYLIMINES

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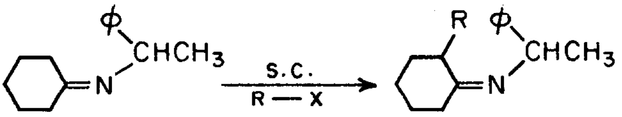
Abstract. The lithiation and alkylation of three aldehydes in the form of their α-phenethylimines has been shown to yield chiral α-alkylaldehydes of 67-70% optical purity.

We recently observed some unusual stereochemical preferences associated with lithiated ketimines (1) and aldimines (2). Both carbonyl derivatives underwent lithiation alpha to the "carbonyl" carbon to give exclusively the syn derivative, which, in the case of cyclohexanone imines, gave axial substitution only. In the recent past, the use of imines in asymmetric synthesis has been elegantly demonstrated by the work of Meyers (3). Cyclic ketimines derived from 1-methoxy-2-amino-3-phenylpropane were transformed to ketones of high enantiomeric excess (≥ 80%), a result attributed to the presence of the chelatable alkoxy substituent. Aldimines exhibited less asymmetric induction, providing alkylated aldehydes having up to 58% ee. Aldehydes of much higher optical purity (up to 87%) were obtained by Enders and Eichenauer (5) via alkylation of a chiral hydrazone. In view of our observations of completely syn and completely axial alkylation of ketimines we have examined more extensively (6), the asymmetric induction in the reactions of ketimines and aldimines of α-phenethylamine. Such studies assess the importance of a donor substituent in the amine moiety re asymmetric induction as well as examine the potential utility of α-phenethylamine (commercially available in either enantiomeric form) as the imine precursor.

We first examined the stereoselectivity in the methylation of cyclohexanone N-α-phenethylimine as a function of a variety of reaction conditions, i.e., 1 → 2a, b using ^{13}C nmr (7).



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2 a) $R=CH_3$, b) $R=C_2H_5$

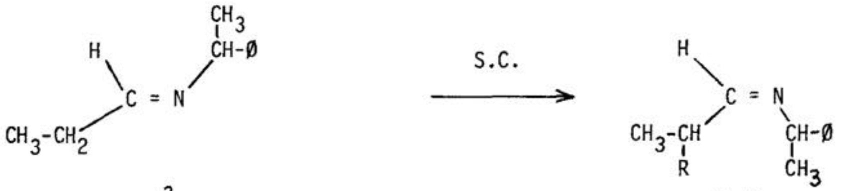
Table 1: Asymmetric Induction in Alkylation of 1.

Reaction Conditions		Diastereomer Ratio
Std. Conditions[a]		2.0
"	($MgBr_2$, 1 eq , CH_3I)[b]	3.2
"	(TMEDA, 1-1 eq,CH_3I)[b]	2.5
"	(HMPA, 1 eq , CH_3I)[b]	2.0
"	($(CH_3)_2SO_4$)	1.3
"	(C_2H_5I)	1.4
"	(C_2H_5Br)	2.1

[a] "Std. Conditions" represents formation of anion using 1.05 eq LDA in THF at 0° for 60 min followed by addition of alkyl halide at -78°C, a reaction time of 60 min before warming to 0°, removing solvent and examining the spectrum of crude product. [b] Concurrent with this work, added $MgBr_2$ was found to affect the asymmetric induction in the alkylation of chiral amides (10).

The results given in Table 1 reveal the alkylation reaction to be very sensitive to the particular conditions and, in the case of reaction in the presence $MgBr_2$, the potential to produce ketone of up to 52% optical purity. Since this amount of asymmetric induction falls far short of that achieved by Meyers we turned our efforts to the alkylation reactions of propionaldimine, 3 , as summarized in Table 2. It can be seen that, under certain conditions, the best of which involves lithiation plus addition of 1 equiv of magnesium bromide, the benzylation proceeds in a highly stereoselective manner, and different optimum conditions were obtained for

Table 2: Alkylation of 3



3

4a,b,c

a) R = CH_2 Ø

b) R = n-C_6H_{13}

c) R = $CH(CH_3)_2$

Reaction Conditions		Diastereomer Ratio[b] 4a	4b	4c
Std. Conditions	(lithiation at -20°)	1.3	2.5	2.5
"	(HMPA, 1 eq)	2.7	4.6	8.2
"	(plus $MgBr_2$, 1 eq)	5	3.1	no rx
"	(" $MgBr_2$, 10 min lithiation at 0°)	5.7	-	
"	(" $MgBr_2$, HMPA 1 eq each)	4.3	5.5	no rx
"	(" $MgBr_2$, 1 eq in diethyl ether)	0.7	no rx	

[b] diastereomer ratios for 4a and 4c were determined by ^{13}C; for 4b the figures were derived from observed rotation of pure product.

other alkyl halide reactions. We therefore conducted the three alkylation reactions followed by hydrolysis using optically pure (-)-3 and the optimum conditions for each alkylation. Table 3 presents the yields and optical purity of each pure aldehyde and, for comparison, those of Enders and Meyers for the same aldehydes. In spite of its lack of a chelating structural component, (-)-3 gives aldehyde of higher optical purity in higher yield than that obtained by Meyers.

Table 3: Aldehydes from S(-) 3

Compound (Config)[a]	Yield[b] (Optical Purity)[c]		
	This Work	Ref. 5	Ref. 3
4 a (S)	88(67)	62(82)	
4 b (S)	87(69)	61(87)	70(58)
4 c (S)	70(70)	60(57)	

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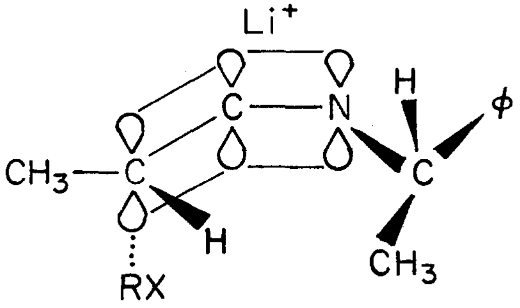
[a] All literature on the configurations and rotations of 4 a-c are given in Ref. 5.
[b] Yields are with reference to distilled product. [c] Optical purities were determined by rotations using solutions of 4 a (c 3.7, acetone), 4 b (c 11.4, $CHCl_3$), 4 c (c 5.4, $CHCl_3$).

Although our yields also exceed those reported by Enders (5,8), in two of three cases, his hydrazone route to the chiral aldehydes 4 a-c offers better optical purity and for this reason probably will prove superior for future aldehyde preparations. Nevertheless, it is clear that α-phenethylimines provide a convenient alternative method for the preparation of chiral aldehydes and ketones.

It is interesting to note that all models previously proposed (3,4,5,9) for the transition state in the alkylation of imines involve chelation of the lithium ion between the alkoxy substituent and the lone pair on the nitrogen of the imine. Since chelation is not essential in our reactions we propose a model which involves the aza-allylic anion, 5, whose delocalized character is required to explain its observed stability and its spectral characteristics (9). This intermediate (10), is depicted below in the syn configuration and, as shown for related imines (9), has the E configuration at the partial C-C double bond.



5

Since the imines derived from S(-) α-phenylethylamine gave aldehydes having an excess of S configuration,5 shows the attack by R-X on the side having bulkier imine methyl group. The most plausible explanation for this behaviour would require this substituent to induce location of the lithium ion on the si face of the anion, which would then undergo alkylation from the re side (11). Differences between 5 and previous models may exist, reflecting basic differences in structure and chelating ability. Considerably more evidence will be required before distinctive merits of the proposed models can be established.

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References and Notes

1. R.R. Fraser, J. Banville and K.L. Dhawan, J. Am. Chem. Soc., 100, 7999 (1978).
2. R.R. Fraser and J. Banville, J. Chem. Soc. Chem. Commun. 1979, 47.
3. A.I. Meyers, D.R. Williams and M. Druelinger, J. Amer. Chem. Soc., 98, 3032 (1976); A.I. Meyers, G.S. Poindexter and Z. Brich, J. Org. Chem., 43, 892 (1978); A.I. Meyers, and D.R. Williams, J. Org. Chem., 43, 3245 (1978); see also A.I. Meyers, Accts. Chem. Res., 11, 375 (1978).
4. J.K. Whitesell and M.A. Whitesell, J. Org. Chem., 42, 377 (1977); S. Hashimoto and K Koga, Tetrahedron Lett., 1978, 573.
5. D. Enders and H. Eichenauer, Tetrahedron Lett., 1977, 191; see also Angew. Chem. Int. Eng. Ed. 15, 549 (1976).
6. The first example of alkylation of a chiral metallated ketimine, specifically the bromomagnesium derivative of cyclohexanone N-isobornylimine described the formation of 2-methylcyclohexanone having 72% optical purity (D. Méa-Jacheet and A. Horeau, Bull Soc. Chim. Fr., 1968, 4571. A subsequent study of the lithiation and methylation of the α-phenethylimine of cyclohexanone reported product having only 26% optical purity (M. Kitamoto, K. Hiroi, S. Terashima and S. Yamada, Chem. Pharm. Bull., 22, 459 (1974)).
7. In the ^{13}C nmr spectra of 2 and 4 measured as crude reaction products at -20°C, the signals for the carbon attached to nitrogen and that at the alkylation site exhibited separate resonances for the two syn diastereomers whose ratios gave a measure of the asymmetric induction (considered to be accurate to ± 5%).
8. D. Enders and H. Eichenauer, Angew. Chem., in press, described the synthesis of optically active 4-methylheptan-3-one, a natural pheromone, using their chiral hydrazone route (5) to obtain a sample having > 98% optical activity. We thank Professor Enders for a preprint describing this remarkable accomplishment.
9. H. Ahlbrecht, E.O Düber, D. Enders, H. Eichenauer and P. Weuster, Tetrahedron Lett., 1978, 3691.
10. We have not attempted to depict the effects of the macroscopic environment such as solvation and aggregation. For example the effects of both $MgBr_2$ and HMPA, though very significant, were variable in the three alkylations studied and thus give no clear indication of their role.
11. Implicit in this explanation is the necessity for alkylation to be much faster than rearrangement of the lithium cation from the si to re face.
12. M. Larcheveque, E. Ignatova and T. Cuvigny, Tetrahedron Lett., 1978, 3961.

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