# Asymmetric Syntheses from Terpene Alkanolamines. Formation of Optically Active 2-Methyloctanal

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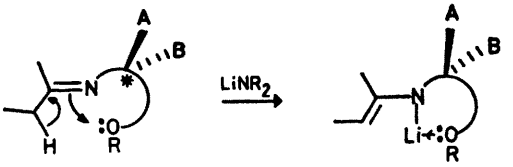
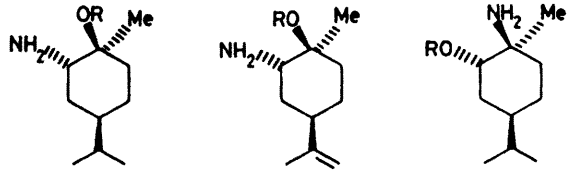
*Summary* Metallation and alkylation (MeI) of the aldimines derived from various terpene methoxy amines and octanal[1] produce, after hydrolysis, *S*(+)-2-methyloctanal in 11—75% enantiomeric excess.

AMONG the more successful asymmetric syntheses described recently is the alkylation of chiral imines *via* their lithio anions producing α-substituted ketones and aldehydes in



60—100% enantiomeric excess (e.e.).[1-3] The imines employed were derived from natural amino acids [*e.g.* from phenylalanine *via* (**6**)[3] and from proline *via* (**7**)[4]] or synthetic amino acids, (**8**).[5] All these syntheses depend upon a chelated metalloenamine (Scheme) to provide a rigid nucleophile with distinct topology. Recent studies have also shown that the geometry about the metalloenamine C–C bond (*E vs. Z*) is important for stereochemically biased alkylation.[3a,6,7]



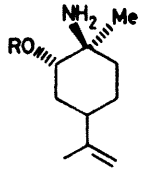
(1*S*,2*S*,4*R*) (1)a, R = H b, R = Me



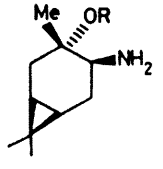
(1*S*,2*S*,4*R*) (2)a, R = H b, R = Me



(1*S*,2*S*,4*R*) (3)a, R = H b, R = Me

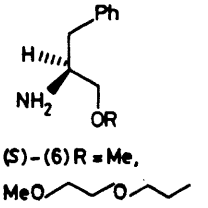


(1*S*,2*S*,4*R*) (4)a, R = H b, R = Me

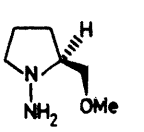


(1*S*,3*S*,4*S*,6*R*) (5)a, R = H b, R = Me

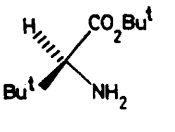
We now report that in addition to the above factors, the nature of the amino group, $R_3CNH_2$ or $R_2CHNH_2$, is critical to the success of the asymmetric alkylation. The chiral alkanolamines (**1a**)—(**5a**) were transformed into their methyl ethers (**1b**)—(**5b**) (KH–MeI) and subjected to the reaction sequence in the Scheme to give, in turn, compounds (**9**)—(**12**). The results of the asymmetric synthesis are given in the Table. It is seen that the secondary carbinamines (**1b**), (**2b**), and (**5b**) are more efficient chiral auxiliary groups than the tertiary carbinamines (**3b**) and (**4b**). The latter lead to 2-methyloctanal in poor enantiomeric purity.



(*S*)-(6) R = Me, MeO

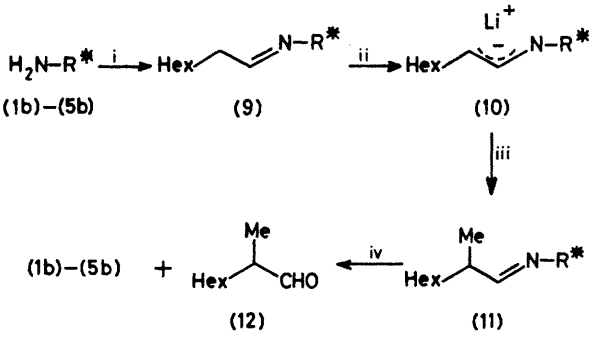


(*S*)-(7)



(*S*)-(8)

Since previous work has shown that the skeletal structures of the chiral alkoxyamines (**6**)—(**8**) have little effect on the efficiency of the asymmetric synthesis[3a,4,5,8] and since similar results were found by varying the alkyl group on the ether,[3a] the nature of the amino group must be an important factor in the synthesis.



SCHEME. i, Octanal, ether, $Na_2SO_4$; ii, lithium 2,2,6,6-tetramethylpiperidide (LiTMP), tetrahydrofuran (THF), 0 °C; iii, MeI, −78 °C; iv, 25% aq. (±)-tartaric acid–THF (2:3). Hex = n-hexyl.

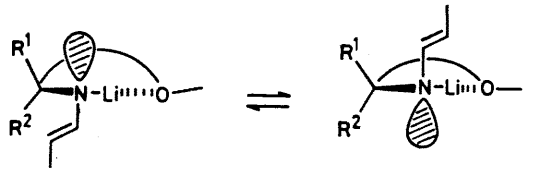
The observation that chiral tertiary carbinamines are less effective in promoting biased alkylation may now be discussed in terms of the conformations (A) and (B) which allow the *N*-lone pair and *N*-vinyl group to lose their preference when $R^2$ is methyl. Thus, the ground state energies for (A) and (B) become similar resulting in alkylation through both species and subsequent loss of stereoselectivity.

In summary, asymmetric C–C bond formation studies through the metalloenamines (**10**) must consider lone pair inversion as well as stereoselective deprotonation and rigid intermediates. Furthermore, it is remarkable that the

TABLE

| Methoxyamines | | | 2-Methyloctanal (12) | | | |
|---|---|---|---|---|---|---|
| Cpd. | B.p./°C (*P*/Torr) | $[\alpha]_{589}$[a]/° | % Yield[b] | $[\alpha]_{589}$[c] | % e.e.[d] | Configuration |
| (**1b**) | 60—70 (0·15) | +31·7 (4·8) | 71 | +15·6 (10·3) | 55·2 | *S* |
| (**2b**) | 60—75 (0·15) | +28·1 (4·9) | 60 | +21·6 (4·7) | 75·2 | *S* |
| (**3b**) | 120—125 (0·5) | +46·6 (1·86) | 80 | + 6·8 (7·4) | 25·6 | *S* |
| (**4b**) | 65—70 (0·15) | +48·2 (7·3) | 76 | − 2·3 (10·3) | 10·7 | *R* |
| (**5b**) | 118—120 (0·2) | +34·4 (7·3)[e] | 57 | +14·8 (6·8) | 54·3 | *S* |

[a] Concentration in ethanol in parentheses. [b] Overall yield from (**1b**—**5b**). [c] Concentration in chloroform in parentheses. [d] % e.e. is based on max $[\alpha]_{589}$ 29·8° (ref. 3c) and $^1$H n.m.r. data; *cf.* A. I. Meyers and Z. Brich, following communication. The % e.e. are corrected for the enantiomeric purities of (**1a**)(97%), (**2a**) (97%), (**3a**) (97%), (**4a**) (97%), and (**5a**) (95—96%).




(**A**) (**B**)

skeletal structures of the chiral amino-ethers play an insignificant role in these processes in view of the belief that steric bulk was a prime requisite for success.

We thank the National Science Foundation for support, the Swiss Science Foundation for a Postdoctoral Fellowship to Z. B., and the N.I.H. for a Postdoctoral Fellowship to G. W. E.

(*Received*, 16*th February* 1979; *Com.* 157.)

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