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CHIRAL OXAZOLINES IN ASYMMETRIC SYNTHESIS. EFFECT OF SUBSTITUENTS ON ASYMMETRIC INDUCTION

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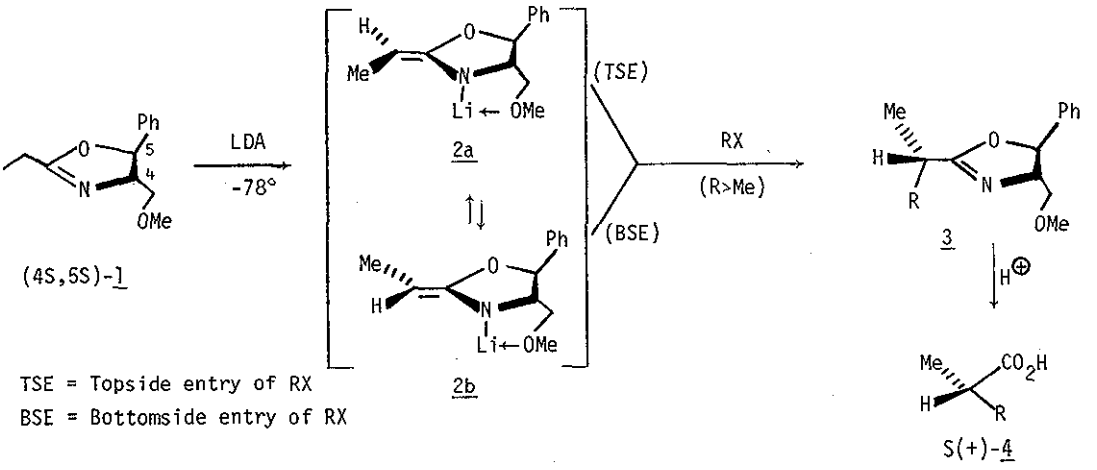
Variation in the 5-substituent on chiral oxazolines leads to large variations in the degree of asymmetric alkylations. These results indicate that both steric and chelating effects are important in achieving high enantiomeric excesses in the product.

The recently described[1] asymmetric synthesis of chiral α-substituted carboxylic acids provided these materials in enantiomeric excess of 70-86%. A number of factors responsible for the rather high ee's observed in this process were considered, but several were still uncertain. The mechanism, based on all the facts in hand at the time, is given in Scheme I. During a search for more accessible chiral oxazolines, several amino acids were examined as suitable alternatives to 1. Reports on the use of L-serine and L-threonine[2,3] as precursors to chiral oxazolines prompted us to examine analogs of 1 with regard to their ability to produce chiral carboxylic acids 4. As depicted in Scheme I, the formation of two equilibrating lithio salts (2a and 2b) which would be alkylated primarily from the bottomside (BSE) via coordination of the alkyl halide with the chelated lithium ion was postulated as the mechanism

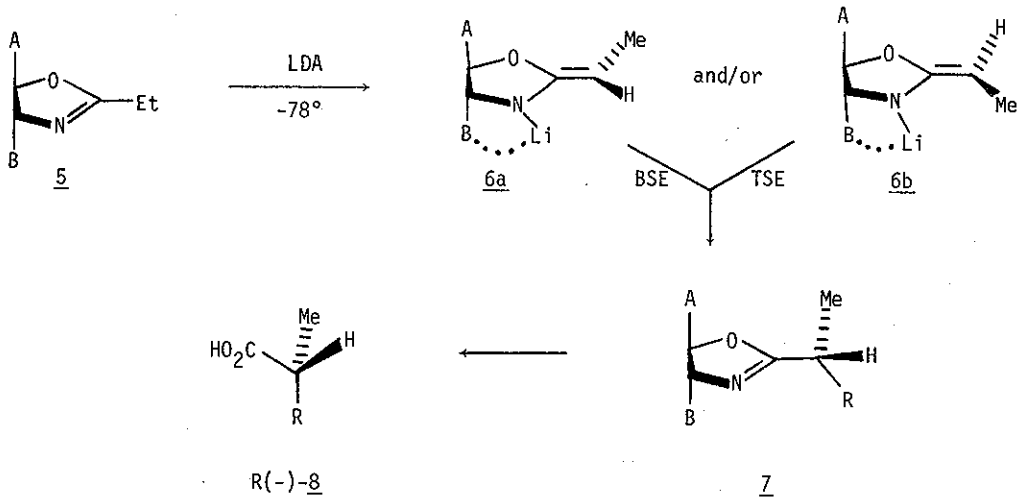
SCHEME I



TSE = Topside entry of RX
BSE = Bottomside entry of RX

of choice. The idea that 2b would react faster than 2a from the bottom was attributed to less non-bonded interaction than the former giving rise to 3 and ultimately to the S-acids 4 which were isolated. This mechanism, as written, precludes any top-side attack on 2a but the role of the phenyl substituents was uncertain. If the coordination of the alkyl halide to the chelated lithium ion is the major factor,[4] the presence of the bulky phenyl group in 2 should have little effect upon the asymmetric alkylation and the chiral acids 4 should possess comparable enantiomeric purity whether the phenyl group is present or absent. It is precisely this effect which was examined and it may now be reported that the nature of the substituent at C-5 in 1 is not trivial.

A series of chiral oxazolines 5 were prepared in 82-99% enantiomeric purity and along with other data in the literature, the % ee of the chiral carboxylic acids were compared (Table I).[5]



Replacement of the phenyl group in 5 by methyl (A=Me) or H (A=H) results in a drastic decrease in the % ee of the chiral acid 8 (entries 1-3, Table I) although the configuration of the predominant enantiomer remains the same. If, instead of alkylation with butyl iodide, benzyl bromide is used (entries 4-6), loss of % ee in 8 is still observed although not as pronounced. Once again, the configuration of the predominent enantiomer remains R. The immediate conclusion to be drawn from this data is the necessity for a bulky substituent at A (i.e. phenyl), for in its absence or

TABLE I Asymmetric Synthesis of 8 as a Function of Substituents on 5

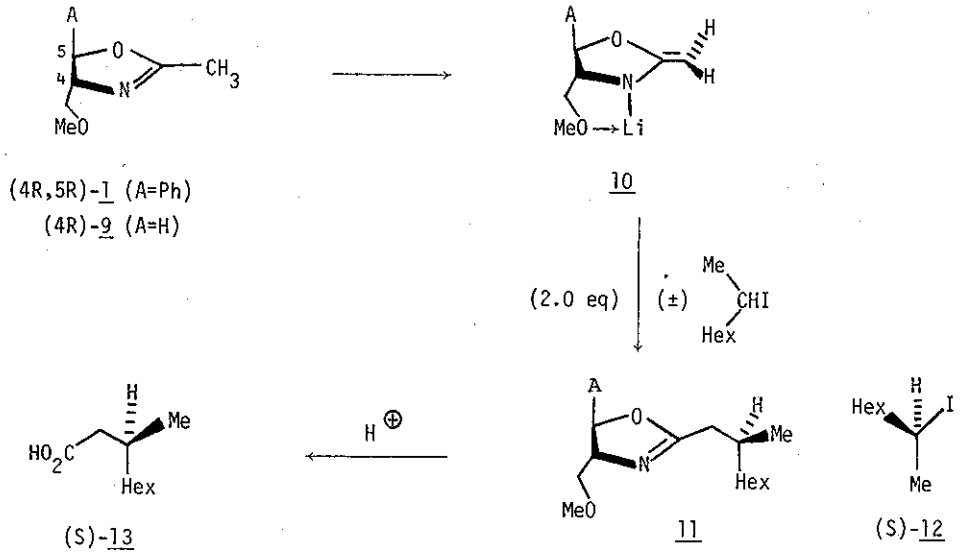
	5				
Entry	A	B	RX	%ee	Configuration
1	Ph	CH_2OMe[a]	n-BuI	78.0	R
2	Me	CH_2OMe[b]	n-BuI	7.2[f]	R
3	H	CH_2OMe[c]	n-BuI	3.5[f]	R
4	Ph	CH_2OMe	$PhCH_2Br$	74.0	R
5	Me	CH_2OMe	$PhCH_2Br$	47.2[f]	R
6	H	CH_2OMe	$PhCH_2Br$	23.7[f]	R
7	H	$C(Me)_2OMe$	n-BuI	75[d]	S
8	Ph	Me	n-BuI	18[e]	R

a) Ref. 1; b) Ref. 5, 82% ee; c) Ref. 5, 83% ee; d) Reported by J. F. Hansen and C. Cooper, J. Org. Chem., 41, 3220 (1976); e) Ref. 1; f) Corrected for 82-83% ee of starting oxazolines.

diminution in bulk, topside entry of the alkyl halide competes readily with bottomside entry. To evaluate the need for chelation of B with the lithium cation, it is noteworthy that previously reported data indicate a significant loss in the % ee of the acid when B = Me (entry 8). On the other hand, the presence of a large substituent for B such as dimethylmethoxymethyl (entry

7) gave a rather high ee for the acid, but with reversed configuration. This is interpreted as topside attack on 6a [A=H, B=$CH_2(Me)_2OMe$)]. The data herein also support the overwhelming presence of lithio salt 6a over 6b since the cisoid interactions are minimized. This would indicate that the lithio salts are present as a thermodynamic mixture as initially suggested.[1,6]

Another study was performed to determine the effect of the C-5 substituent in kinetic resolution of (±)-sec-alkyl halides. In a previous report[7] it was shown that the 4-methoxymethyl-5-phenyl oxazoline 1 possessed chiral recognition as its lithio salt 10 when treated with 2.0 equiv of racemic 2-iodooctane. Recovered



(4R,5R)-1 (A=Ph)
(4R)-9 (A=H)

10

(S)-13
39% ee (A=Ph)
16% ee (A=H)

11

(S)-12

halide 12 was found to be 35-40% enantiomerically pure while the alkylated oxazoline 11, upon hydrolysis gave 3-methyl nonanoic acid 13 in 39% ee. Both 12 and 13 possessed the S-configuration indicating that the R-enantiomer of 2-iodooctane was preferentially alkylated by 10. Repetition of this experiment using the oxazoline 9[8] (from L-serine) gave the S-acid 13 and the S-halide 12 in 14-16% ee. Thus, the absence of the phenyl group in 9 caused at least a 50% drop in the efficiency of the kinetic resolution. This may also be interpreted as allowing topside entry, in the absence of the phenyl group, by either enantiomer of 2-iodooctane since at the underside, there is chirality which possesses preference for the R-halide.

In conclusion, alkylation of chiral oxazolines may occur from the topside or the bottomside if comparable accessibility exists. However, the presence of a large substituent (e.g., phenyl), discourages topside alkylation in favor of entry from the lithium-chelated underside.

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3. R. A. Moss and T.B.K. Lee, J. Chem. Soc. Perkin I, 2778 (1973).

4. This effect is discussed in Ref. 1, structures 24A and 24B.

5. Oxazoline 5 (entries 3, 6) was prepared using L-serine ethyl ester and the imidate of propionitrile according to A. I. Meyers and C. E. Whitten, Heterocycles, 4, 1687 (1976). Oxazoline 5 (entries 2, 5) was prepared using L-threonine ethyl ester and propionitrile imidate using the procedure above; bp 54-57° (5 mm), $[\alpha]_D^{25}$ = 125° (10.5, $CHCl_3$); enantiomeric purity determined as 83% by chiral shift reagent.

6. Recent reports on enolate formation indicate that the kinetic enolates are formed when esters and ketones are metallated with LDA [R. E. Ireland, R. H. Mueller, and A. K. Willard, J. Am. Chem. Soc., 98, 2868 (1976); W. A. Kleschick, C. T. Buse, and C. H. Heathcock, ibid., 99, 248 (1977)]. This phenomenon does not appear to operate in the oxazoline anions and rapid equilibration to the thermodynamic more stable lithio salt (e.g. 2b or 6a) takes place. The use of HMPA in these systems did not change the % ee of the acids isolated.

7. A. I. Meyers and K. Kamata, J. Am. Chem. Soc., 98, 2290 (1976).

8. Bp 56-59° (8 mm), $[\alpha]_D$ 121° (10.1, $CHCl_3$). Enantiomeric purity of 9 was 98±2% by nmr.

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