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SYNTHESIS VIA OXAZOLINES. VII. ASYMMETRIC REDUCTION OF KETONES WITH CHIRAL HYDRIDE REAGENTS

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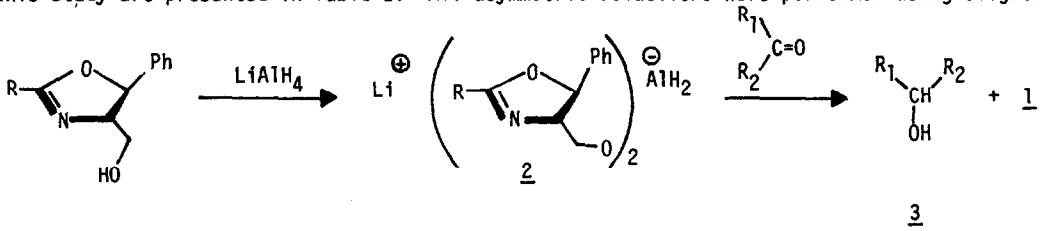
The recent findings that 2-oxazolines are inert to lithium aluminum hydride[1] and the successful implementation of a chiral non-racemic oxazoline as a reagent in asymmetric synthesis[2,3] have prompted a study involving oxazoline-hydrides as chiral reducing agents. Several chiral non-racemic oxazolines 1 were prepared as previously described[2,3] and evaluated with various ketones in order to assess the degree of asymmetric reduction to chiral secondary alcohols 3. The results of this study are presented in Table I. All asymmetric reductions were performed using slightly



1a, R=Me, $[\alpha]_D^{25}$ -150° (c 10.8, $CHCl_3$), mp 63-64°

1b, R=Et, $[\alpha]_D^{25}$ -125° (c 9.7, $CHCl_3$), mp 68-69°

1c, R=i-Pr, $[\alpha]_D^{25}$ -101° (c 9.7, $CHCl_3$), mp 63-65°

1d, R=$PhCH_2$, $[\alpha]_D^{25}$ -44.6° (c 5.4, $CHCl_3$), mp 128-130°

over 2.0 moles of oxazoline carbinol per mole of lithium aluminum hydride since this stoichiometry was found to be optimum. The oxazoline-hydride reagent 2 was treated at various temperatures, using acetophenone as a substrate and the percent asymmetric reduction increased with decreasing

Table I Reduction of Ketones by Chiral Oxazoline-LAH Adduct (2.3:1) in THF

Exp.	Ketone R_1	Ketone R_2	Oxazoline	Reduction T°	Alcohol[a] %	$[\alpha]_D^{25}$[b]	Config.	Optical Purity %	Oxazoline Recovery %
1	Ph	Me	1a	-10°	90	+6.3°	R	14.5[c]	88
2	Ph	Me	1a	-40°	86	+17.6	R	40	69
3	Ph	Me	1a	-60°	91	+14.1°	R	32	81
4	Ph	Me	1a	-78°	79	+3.6°	R	8.3	91
5	Ph	Me	1b	-20°	67	+16.5°	R	38	85
6	Ph	Me	1b	-60°	61	+24.7°	R	57	82
7	Ph	Me	1b	-78°	80	+28.4°	R	65	85
8	Ph	Me	1c	-78°	88	+23.2°	R	53	91
9	Ph	Me	1d	-65°	68	+23.1°	R	53	74
10	Ph	Et	1b	-78°	81	+17.2°	R	62[d]	92
11	Ph	i-Pr	1b	-78°	78	+20.4°[f]	R	43[e]	90
12	α-Tetralone		1b	-78°	89	+1.21[h]	S	3.7[g]	88
13	$PhCH_2$	Me	1b	-78°	93	+0.12	S	0.5[i]	95
14	n-Hex	Me	1b	-78°	95	+0.40	S	4[j]	88
15	n-Hex	Me	1c	-78°	80	-0.55	R	6[j]	87

a) Distilled yields, purity 90-99% by vpc; b) All rotations taken neat unless otherwise specified; c) Based on $[\alpha]_D^{25}$ 43.6° (neat) reported by R. H. Pickard and J. Kenyon, J. Chem. Soc., 99, 45 (1911); d) Based on $[\alpha]_D^{25}$ 27.7° (neat) reported in c); e) Based on $[\alpha]_D^{20}$ 47.7° (ether) reported by P. A. Levene and J. Mikeska, J. Biol. Chem., 70, 355 (1926); f) c 10.0 in ether; g) Based on $[\alpha]_D^{17}$ 32.7° ($CHCl_3$) reported by A. G. Davies and A. M. White, J. Chem. Soc., 3300 (1952); h) c 10.7 in $CHCl_3$; i) Based on $[\alpha]_D^{23}$ 26.2° (neat) reported by C. L. Arkus and P. A. Hallgarten, J. Chem. Soc., 2987 (1956); j) Based on $[\alpha]_D^{25}$ 9.57° (neat) reported by S. J. Cristol, B. Franzus and A. Shadan, J. Amer. Chem. Soc., 77, 2512 (1955).

temperature. In the case of the 2-methyloxazoline 1a, its lack of solubility below -40° (Exp 1-4) was responsible for the drop-off in asymmetric reduction. However, the 2-ethyl derivative 1b (Exp 5-7) was totally soluble at all temperatures and asymmetric reduction of acetophenone gave 1-phenylethanol in 65% optical purity at -78°. The oxazolines 1c and 1d also were soluble at -78° and gave slightly lower optical yields (Exp 8, 9) of alcohol. It

Table II Comparison of Various Asymmetric Reducing Agents. Optical Purities and Configuration of Secondary Alchols

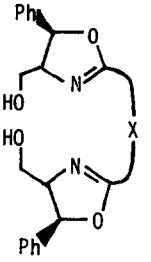
Ketone	LAH-Alkaloid[5]	LAH-monosaccharide[6]	AlH_3-amine[7]	R_3Al[8]	LAH-Darvon[9]	LAH-1b
PhCOMe	48R	71R	84S[a]	6S	68R	65R
PhCOEt	---	46R	---	13S	---	62R
PhCO-i-Pr	---	---	---	44S[b]	30R[c]	43R
α-Tetralone	---		---	0	---	3.7S
$PhCH_2COMe$	3R	---	16S[a]	---	---	0.5S
HexCOMe	6S	25R	---	---	---	4S

a) Reduction yield was 50%; b) Reduction yield was 20%; c) Also obtained 48%ee (R) in 20% reduction yield.

was therefore concluded that 1b at -78° was the reagent of choice since it could be prepared in high yield[1] and exhibited the desired solubility properties. A series of ketones were examined with 2 (R=Et) and found to proceed with varying degrees of success. The phenyl ketones (Exp 10, 11) appear to lead to phenyl carbinols in reasonably high optical yield whereas others (Exp 12-15) although readily reduced at -78° with 2, gave rather low percentages of asymmetric reduction. Other hydrides ($LiBH_4$, BH_3) were also examined with the chiral oxazolines and did not produce any significant improvements in asymmetric reductions. In an attempt to further evaluate the optimum stoichiometry for 1 and LAH, it was found that although 3 moles of 1 would react with LAH, the product did not serve as a reducing agent. Similarly when 2 was treated with 2 moles of ketone, only a 50% yield of carbinol was obtained. Thus the fourth and remaining hydride is presumably residing in a highly hindered environment and therefore incapable of being transferred to a carbonyl carbon. Despite the lack of consistently good asymmetric reduction on various ketones, the oxazoline-hydride reagent is nevertheless competitive with other chiral hydride reagents. Table II sumarizes the efficiency of 1b as compared to other systems. It is important to note that this preliminary survey indicates that optically active alcohols may be

prepared[4] from a single recoverable reagent in optical yields comparable to those obtained from a variety of different systems. At this time we reserve comment on the exact nature of the oxazoline-hydride reagent pending further study.[10]

We are currently examining various modifications of oxazoline-carbinols (e.g. 4) in anticipation of more pronounced asymmetric reduction.



4 X = $-(CH_2)_n$, O, NR

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4. A general procedure is as follows: LAH (20 mmoles) in 80 ml THF, cooled to -78° is treated portionwise (via Gooch tubing) with 1b (46 mmoles) over 45 min. Complete hydrogen evolution is attained after stirring for 15 min. The ketone (10 mmoles) is added (-78°) and stirred for 2 h. The mixture is treated successively with 0.75 ml water, 0.75 ml 15% NaOH, and 2.25 ml water, the aluminum salts were removed and washed with 250 ml ether and combined with the THF solution. The oxazoline was removed by shaking with ice-cold 0.3N HCl and the carbinol recovered by concentration of the ether layer.

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10. For a discussion on the structures of chiral hydride reagents see Ref. 9 and J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice-Hall, 1971, pp 202-218.