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CHROMIUM COMPLEXED CARBINOLS AS HIGHLY EFFECTIVE AUXILIARIES FOR USE IN ASYMMETRIC INDUCTION : REDUCTION OF α-KETOESTERS

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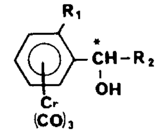
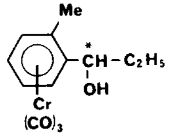
Abstract : High percentages of asymmetric induction are obtained during reduction of pyruvate and phenylglyoxylate esters of chromium complexed carbinol 1a: 75% with $NaBH_4$ and 85% to 90% with L-selectride.

We recently reported (1) that the chromium complexed carbinol 1a can impart exceptionally high level of diastereoface selection during Prelog-type synthesis.

1

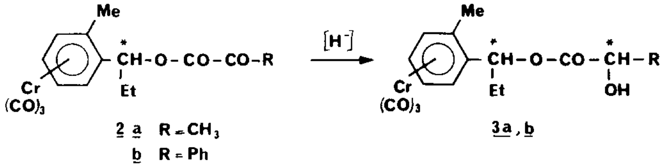


1a



(+)1SS $[\alpha]_D^{20}$ max = +36° (2)
(c 0.6,$CHCl_3$)

We,now, want to report reduction of α-ketoesters using the same alcohol 1a as chiral auxiliary, according to the following equation :

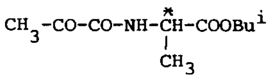


Different reducing agents have been examined, table 1. The diastereomer ratios have been determined on crude products by ^1H NMR (200MHz, Bruker WP 200 SY) and two examples are given on figure 1.

No general trend could yet be established, and the role of the cation is not clear.

The high percentage of asymmetric induction (75%) obtained with $NaBH_4$ in the case of phenylglyoxylate ester 2b is interesting and unusual compared with the litterature results (3), but apparently temperature in this case has little effect on the asymmetric induction, which thus could not be improved.

The very poor asymmetric induction (8%) obtained with $NaBH_4$ in the case of pyruvate ester 2a must be noticed as recent litterature results (4,5) were somehow better : 33% in the case of (-)-8-phenylmenthylpyruvate (4) and 39% to 42% in the case of amide 4 (5).



$CH_3\text{-CO-CO-NH-}\overset{*}{C}H(CH_3)\text{-COOBu}^i$ 4

However it has been found that L-selectride (6) leads to very high percentage of asymmetric induction, 85% to 90%,with both pyruvate ester 2a and phenylglyoxylate ester 2b. Surprisingly, potassium tri-isopropoxyborohydride (4) leads to a quite lower percentage of asymmetric induction with (-)-8-phenylmenthylphenylglyoxylate (50%) than with (-)-8-phenylmenthylpyruvate (90%).

As the most interesting result is the 75% of asymmetric induction obtained in the case of phenylglyoxylate ester 2b with readily available and less expensive $NaBH_4$, we are looking for chromium complexed carbinols 1 bearing different R_1 and R_2 groups in order to improve the percentage of asymmetric induction. 85% d.e. has already been obtained with carbinol 1b (R_1 = Me, R_2 = iPr).

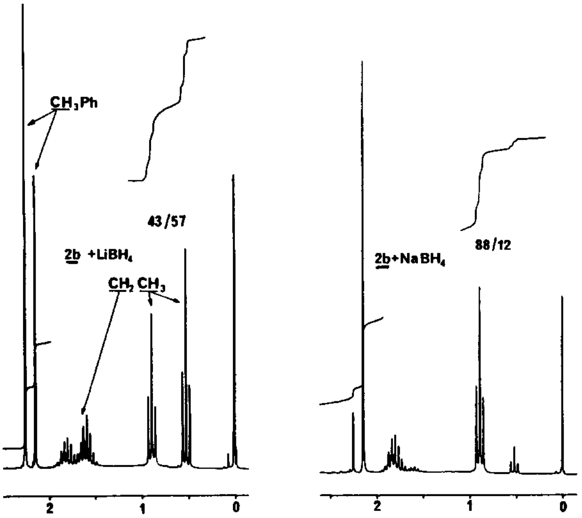
Table 1 : Reductions* of α-ketoesters 2a and 2b .

ketoester	reagent	Yield %	react. t° C	diastereomer ratio	d.e. %
2a R = CH_3	$LiBH_4/EtOH$	80	-70°	44/56	12
	$NaBH_4/EtOH$	70	-70°	46/54	8
	$KBH_4/EtOH$	78	-70°	32/68	36
	$LiB(CH(CH_3)C_2H_5)_3H/Et_2O$	75	-70°	8/92	84
2b R = Ph	$LiBH_4/EtOH$	75	-70°	43/57	14
	$NaBH_4/EtOH$	85	-100°	85/15	70
	" "	70	-70°	88/12	76
	" "	65	+20°	82/18	64
	$NaBH_4/THF$	70	-70°	89/11	78
	$KBH_4/EtOH$	85	-70°	58/42	16
	B_2H_6/THF	90	-70°	58/42	16
	$LiB(CH(CH_3)C_2H_5)_3H/Et_2O$	90	-70°	95/5	90

** A solution of complexed α-ketoester (0.3 g, 0.7 10^{-3}mol, in 3ml of EtOH) is added dropwise to a stired solution of $NaBH_4$ (0.053 g, 1.4 10^{-3}mol in 10ml of EtOH) at -70°. The mixture is maintained at -70° over a period of 30mn, then poured into 50ml of water. After extraction with ether the organic layer is dried on sodium sulfate. Evaporation of the solvent give the crude complexed α-hydroxyester.*

Figure 1

^{1}H NMR of 3b



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