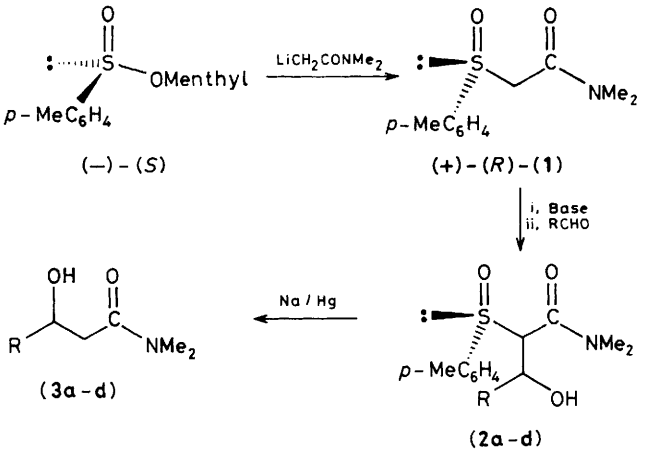
An Enantiomerically Pure α-Sulphinyl-*N,N*-dimethylacetamide: a New, Efficient Reagent for Enantioselective Aldol-type Condensation

Rita Annunziata, Mauro Cinquini, Franco Cozzi, Fernando Montanari, and Angelo Restelli
Centro CNR and Istituto di Chimica Industriale dell'Università, Via Golgi 19, 20133 Milano, Italy

Asymmetric synthesis (up to 99%) of β-hydroxy-*N,N*-dimethylacetamides was achieved starting from aldehydes and an optically active sulphoxide containing synthon, the sense of chiral discrimination depending on the intermediate metal enolate.

Exceptionally high levels of both diastereo- and enantioselectivity have recently been reported by Evans[1] using boryl enolates of chiral propionyl imides in an aldol condensation. Unfortunately, the corresponding acetate enolate equivalents



a R = Me
b R = Bu^i
c R = Pr^i
d R = Bu^t

showed much lower degrees of chiral discrimination. To circumvent this problem an easily removable methylsulphide group was inserted in the enolate synthon and thus excellent enantioselections were achieved.[1]

The insertion of an optically active sulphinyl group into an acetamide moiety could in principle secure the necessary substitution on the enolate and simultaneously provide the source of chirality. Chiral sulphur derivatives such as α-sulphinyl-hydrazones[2] and -esters[3–5] indeed proved to be effective in promoting stereoselective aldol-type condensations.

Treatment of α-lithio-*N*,*N*-dimethylacetamide[6] with diastereoisomerically pure (−)-(*S*)-menthyl toluene-*p*-sulphinate[3] gave the α-sulphinyl-amide (**1**), $[\alpha]_D^{22}$ + 194.7° (*c* 1, in $CHCl_3$), m.p. 63—64 °C (from di-isopropyl ether) in 83% yield. Compound (**1**) was shown to be enantiomerically pure by ^{1}H n.m.r. spectroscopy in the presence of the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III), Eu(hfc)$_3$. The (*R*) absolute configuration at the sulphur atom in (**1**) can be inferred from data on related Andersen-type syntheses.[7]

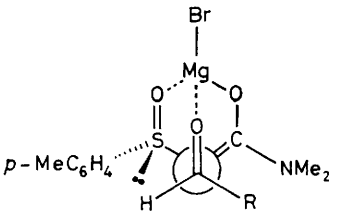
The metal enolate derived from (+)-(*R*)-(**1**) was allowed to react with aldehydes to afford the crude adducts (**2a**—**d**), which were desulphurized (10% Na/Hg, NaH_2PO_4, MeOH) to give the optically active β-hydroxy-amides (**3a**—**d**). Yields, optical rotations, and enantiomeric excesses (e.e.) are reported in Table 1.

Low to medium levels of enantioselection (e.e. up to 47%) were achieved using Bu^{n}Li as base. However, with magnesium enolates a dramatic effect was observed; chiral discrimination was much higher (e.e. ⩾90—99% under the best conditions) and, most strikingly, its sense was reversed. 1.1 : 1 and 0.55 : 1 were the best base : substrate molar ratios, and 3 and 60 min were the optimum condensation times for Bu^{n}Li and Bu^{t}MgBr, respectively. The addition of hexamethylphosphoramide (HMPA) to the lithium enolate reversed and lowered at the same time the enantioselectivity. Independent of the nature of the base less bulky aldehydes underwent a more enantioselective face differentiating reaction. This behaviour of the sulphinyl-amide (**1**) is in contrast with that observed[1–3] for other sulphur containing chiral enolate equivalents. The absolute configuration of the β-hydroxy-amides (**3**) was unambiguously determined for (**3c**) as (−)-(*S*) by chemical correlation with (−)-(*S*)-3-hydroxy-4-methylpentanoic acid[1] (CH_2N_2, Et_2O; Me_2NH, MeOH).

Table 1. Results of the enantioselective condensation of (+)-(*R*)-(**1**) with aldehydes RCHO.

R[a]	Base	Yield[b] (%)	$[\alpha]_D^{22}$/° [c]	Enantiomeric[d] excess (%)
Me	Bu^{n}Li[e,f]	65	+30.3	47
Bu^i	Bu^{n}Li[e,f]	77	+14.3	45
Pr^i	Bu^{n}Li[e,f]	77	+21.6	34
Pr^i	Bu^{n}Li[e,g]	78	+19.4	31
Pr^i	Bu^{n}Li[f,h]	40	+10.6	17
Bu^t	Bu^{n}Li[e,f]	20	+ 6.6	8
Pr^i	Bu^{n}Li[e,f,i]	78	−11.9	19
Me	Bu^{t}MgBr[g,j]	68	−65.0	⩾99
Bu^i	Bu^{t}MgBr[g,j]	71	−31.3	98
Bu^i	Bu^{t}MgBr[e,f]	73	−28.4	89
Pr^i	Bu^{t}MgBr[f,j]	62	−53.5	85
Pr^i	Bu^{t}MgBr[g,j]	66	−59.7	95
Pr^i	Bu^{t}MgBr[e,f]	63	−43.3	69
Bu^t	Bu^{t}MgBr[g,j]	56	−70.9	90

[a] All reactions carried out at −78 °C under argon with 0.02 M solution of (+)-(*R*)-(**1**) in tetrahydrofuran. Metallation time 30 min. Bu^{n}Li, 1.3 M solution in hexane; Bu^{t}MgBr, 1.0 M solution in diethyl ether. [b] Yield of (**3a**—**d**) starting from (**1**); product isolated by column chromatography on silica gel. [c] *c* 1, in chloroform. [d] Determined by ^{1}H n.m.r. spectroscopy with the aid of the chiral shift reagent Eu(hfc)$_3$. [e] 1.1 mol. equiv. [f] Condensation time 3 min. [g] Condensation time 60 min. [h] 2.0 mol. equiv. [i] In the presence of 3 mol . equiv. of HMPA. [j] 0.55 mol. equiv.



(4)

Although more information is necessary to rationalize fully the mechanism of this process, the extent of asymmetric synthesis observed for magnesium enolates is sufficiently high to suggest a rigid model for the transition state, (**4**), similar to that proposed for α-sulphinyl esters.[3] As far as (**4**) is concerned it must be noted that: (i) chelation of magnesium by the sulphinyl oxygen favours the (*Z*) geometry commonly accepted for amide enolates, (ii) the correct chirality of the resulting β-hydroxy-amides can be predicted, and (iii) the model could account for the decrease in stereoselection observed on increasing the steric demand of the aldehyde R residue, owing to greater interaction with the dimethylamino group.

Received, 23rd June 1983; Com. 838

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