

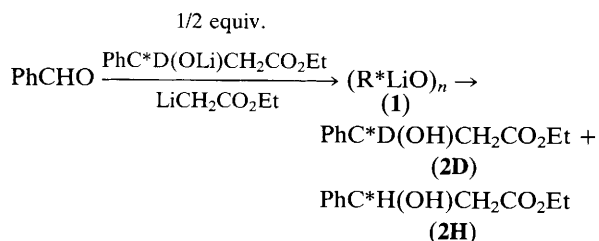
Enantioselective Autoinduction in the Aldol Condensation of Ethyl Acetate and Benzaldehyde: Selective Precipitation of an Optically Inactive Li–O-aggregate

Albert H. Alberts† and Hans Wynberg*

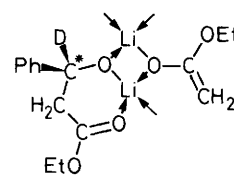
Department of Chemistry, University of Groningen, Nijenborgh 16, Groningen, The Netherlands 9747AG

The influence of half an equivalent of optically active (–)-(S)-ethyl [3-²H]3-phenyl-3-hydroxypropanoate on the stereochemical course of the aldol condensation of ethyl acetate and benzaldehyde was studied; an enantioselective autoinductive effect on the formation of the second equivalent of hydroxyester of 18% (–100 °C) was determined in favour of the opposite (+)-isomer; separate work-up of precipitated Li–O-aggregate revealed that the (+)-isomer is predominant in the solid phase [enantiomeric excess (e.e.) 68%]; the mother liquor is considerably enriched in the (–)-isomer (e.e. 59%).

We have defined the influence of the product on asymmetric C–C bond formation as the principle of enantioselective autoinduction, and we have demonstrated this principle to be operative under homogeneous stoichiometric and catalytic conditions.¹ Now we describe the enantioselective autoinductive effect of optically active (–)-(S)-ethyl [3-²H]3-phenyl-3-hydroxypropanoate on the aldol condensation of ethyl acetate and benzaldehyde (Scheme 1).²



Scheme 1



(3)

The deuteriated hydroxyester (**2D**) (81% optical purity³) (4 mmol), and ethyl acetate (4 mmol) were added to lithiohexamethyldisilazane⁴ (8 mmol) in dry tetrahydrofuran (thf) (8 mmol) (nitrogen atmosphere) at –70 °C (bath temperature). After 30 min, benzaldehyde (4 mmol) was introduced and the initially homogeneous solution was left in the cooling bath overnight (15 h, final bath temperature –35 °C). The heterogeneous mixture (precipitation of a white crystalline solid started after 4–5 h) was poured into dilute HCl and extracted three times with ether. After washing with aqueous sodium hydrogen sulphite and water and evaporation of solvents, the mixture of hydroxyesters (**2D**) + (**2H**) was

† Present address: Technical University Eindhoven, P.O. Box 513, Eindhoven, 5600MB Eindhoven, The Netherlands.

subjected to molecular distillation until constant rotation (100 °C, 0.1 mmHg). The ratio of (2H)/(2D) was determined by integration of the methine signal of (2H) and the methylene signal of (2D) + (2H). The enantiomeric excess (e.e.) of (2H) in the mixture was determined by comparison of the rotation of (2D) + (2H) with a stoichiometrically identical mixture of (2D) and racemic (2H). The autoinductive effect was counterproductive: an e.e. of 12% at -70 °C and 18% at -100 °C (initial *T*) in favour of the (+)-isomer of (2H) was found.

Separate work-up of the crystalline deposit and the mother liquor revealed more detail: filtration under nitrogen produced a hygroscopic material, which correctly analysed for $\{[\text{LiO-PhCHCH}_2\text{CO}_2\text{Et}]_n \cdot 1/4\text{thf} \text{ (1)}\}$ (decomp. >200 °C). The solvent ligand could be removed after treatment with hot hexane, leaving the complex as a white amorphous powder. Absence of solvent and silazane ligand indicated a tetrameric Li-O-aggregate.⁵ Hydrolytic work-up of this solid phase liberated an approximately 1:1 mixture of (2D) + (2H), [*c.f.* 43%, specific rotation -3.8°, expected -21.6° when (2H) is racemic] giving an e.e. for (2H) of 68% in favour of the (+)-isomer (-70 °C initial reaction temperature). Apparently, the diastereoisomer of (1) with an internal centre of symmetry was preferentially precipitated. This was confirmed by work-up of the supernatant: an e.e. for (2H) of 59% in favour of the (-)-isomer was found (specific rotation -36.9°, *c.f.* 36%).

Addition of tetramethylethylenediamine (TMEDA) (2–10 equiv.), with the intention of simulating standard conditions of asymmetric induction with chiral N-auxiliaries, invariably led to the same result: precipitation of a diastereoisomeric complex carrying an excess of (+)-isomer, leaving behind a mother liquor enriched with the (-)-isomer. The yield of (2D) + (2H) and the e.e. for (2H) decreased with increasing concentration of TMEDA [e.e. for (2H) was negligible with 10 equiv. of TMEDA].

We believe that autoinduction takes place in solution (at room temp. unstable) *via* a mixed cluster (3) in which the hydroxycarbonyl ligand influences the stereochemistry of addition of aldehyde to the enolate ligand.

From the perspective of asymmetric synthesis in general we conclude that collective work-up of heterogeneous product mixtures (and/or warm-up to a homogeneous solution at room temp.) has to be avoided at all times. In the case presented,

the overall counterproductive autoinduction seems to forbid 100% enantioselectivity under conditions of 1:1 Li-enolate and carbonyl compound with less than 10 equiv. of auxiliary ligand. In reactions with very high enantioselectivity, however, one suspects synergy of auto- and auxiliary-induction in aggregates of type (3).

The results presented here imply that partially enriched products from a variety of enantioselective syntheses with chiral ligands can be upgraded simply by preparing an alkali metal alkoxide complex (in a final purification step) and precipitating diastereoisomeric optically inactive aggregates.

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- Prepared from hexamethyldisilazane (8 mmol) and *n*-butyl-lithium (8 mmol, 2.5 M in hexane): M. Rahtke, *J. Am. Chem. Soc.*, 1970, **92**, 3222.
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‡ The relation of e.e. and specific rotation of various mixtures of (2D) and (2H) is linear. Compound (2D) does not racemize under the reaction conditions. The optical characteristics of (2D) and (2H) are identical within experimental error.