

Asymmetric Self-catalytic Reaction. Self-production of Chiral 1-(3-Pyridyl)alkanols as Chiral Self-catalysts in the Enantioselective Addition of Dialkylzinc Reagents to Pyridine-3-carbaldehyde

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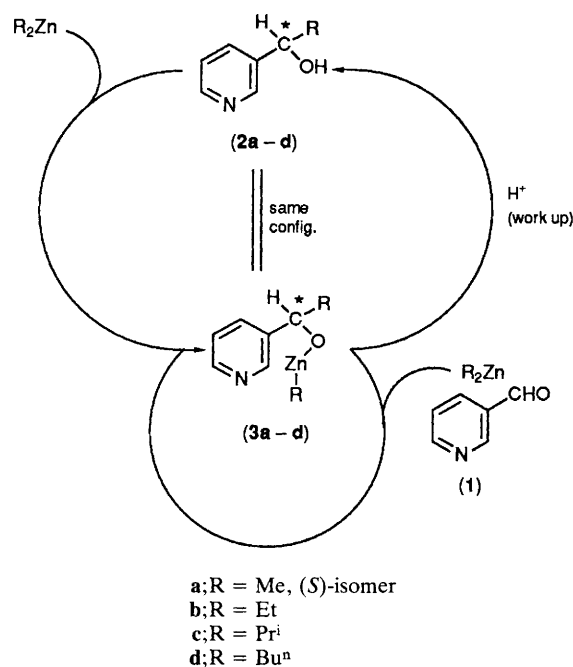
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Optically active 1-(3-pyridyl)alkanols, chiral self-catalysts, produced themselves of the same configuration in the enantioselective addition of dialkylzinc reagents to pyridine-3-carbaldehyde.

Increasing interest has been centred on catalytic carbon-carbon bond forming reactions.¹ However in nearly all cases reported, the structures of the chiral catalysts and the products are *different*. If the structures of the product and the chiral catalysts were the *same* (chiral self-catalyst), the reaction

system would become an interesting real self-production of chiral molecules. Although the implication of asymmetric self-catalysis has been described,² no apparent example is known.³

We are continuing to study the enantioselective synthesis of



Scheme 1

amino-alcohols by asymmetric reduction of ketones⁴ and by asymmetric alkylation of aldehydes,⁵ and we now report an example of an asymmetric self-catalytic reaction in which a chiral molecule plays the role of a chiral catalyst to afford the same chiral molecule of the same configuration. When pyridine-3-carbaldehyde (**1**) (1 mmol) was treated with di-isopropylzinc (2 mmol) using (-)-2-methyl-1-(3-pyridyl)propan-1-ol (**2c**) (0.030 g, 20 mol%), [α]_D²² -35.7° (*c* 2.3, MeOH) (86% enantiomeric excess, e.e.)[†] as a chiral catalyst, (-)-(**2c**) (0.132 g, 47% e.e., determined by HPLC using a chiral column) was obtained.[‡] This result shows that (-)-(**2c**)

[†] Prepared from the reaction of pyridine-3-carbaldehyde and di-isopropylzinc using (1*S*,2*R*)-(-)-*N,N*-dibutylnorephedrine^{5,6} as a chiral catalyst.

[‡] Pr₂Zn (2 ml of 1 M hexane solution) was added to a toluene solution (2 ml) of (-)-(**2c**) (0.2 mmol) at room temperature. After 20 min, (**1**) (1.0 mmol) was added, then the mixture was stirred at room temperature for 2 h. The mixture was cooled to 0 °C, and quenched by the addition of HCl (1 M; 5 ml). The mixture was adjusted to pH 8–9 by the addition of satd. aq. NaHCO₃, and the precipitate was filtered off. The filtrate was extracted with AcOEt (4 × 20 ml), dried (Na₂SO₄), and evaporated under reduced pressure. The residue was purified by TLC (silica gel, eluant AcOEt–MeOH, 20 : 1), followed by bulb-to-bulb distillation (140 °C at 2 mmHg). HPLC analysis was performed with Daicel Chiralcel OD, eluant 10% propan-2-ol in hexane, flow rate 0.2 ml/min, UV detector (254 nm), retention time 62.7 min for major isomer (-)-(**2c**), 70.3 min for minor isomer (+)-(**2c**).

acts as a chiral self-catalyst to produce itself with retention of configuration [(-)-(**2c**), 0.102 g, 67% yield, 35% e.e.].[§] In a similar manner, (-)-1-(3-pyridyl)propan-1-ol (**2b**) (20 mol%, 56% e.e.) produced itself [(-)-(**2b**) (66%, 14% e.e.)] in the enantioselective addition of Et₂Zn to (**1**). Asymmetric self-catalytic reaction was also observed in methylation [(*S*)-(-)-(**2a**) of 42% e.e. afforded (*S*)-(-)-(**2a**) of 7% e.e.] and in butylation [(-)-(**2d**) of 47% e.e. afforded (-)-(**2d**) of 6% e.e.].

The mechanism of this reaction may be as follows (Scheme 1). Chiral compounds (**2a–d**) are considered to form the chiral zinc monoalkoxides (**3a–d**), which catalyse the enantioselective addition of R₂Zn to (**1**) and the amount of (**3a–d**) increases. The configuration of the asymmetric carbon atom bonded to the hydroxy group in the chiral ligand is one factor which determines the sense of the asymmetric induction.⁷ Acidic hydrolysis of (**3a–d**) during work-up afforded increased amounts of chiral (**2a–d**).⁸

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[§] The same (-)-(**2c**) (86% e.e.; 20 mol%) catalyses the enantioselective addition of Et₂Zn to benzaldehyde in hexane at room temperature to afford (*S*)-(-)-1-phenylpropanol of 16% e.e. in 87% yield.