

Presence or absence of a nonlinear effect according to the asymmetric catalyst preparation in the alkylation of benzaldehyde

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This article is dedicated to the memory of John Osborn, who made brilliant contributions to the area of organometallic catalysis.

Abstract – The addition of Et_2Zn on benzaldehyde in the presence of a stoichiometric amount of $\text{Ti}(\text{O}i\text{-Pr})_4$ catalysed by (1*R*,2*R*)-bis(trifluoromethanesulfonamido)-cyclohexane **1a** has been revisited. A nonlinear effect was present or absent, depending on the catalyst preparation. An asymmetric amplification has been observed when $\text{Ti}(\text{O}i\text{-Pr})_4$ was added to **1a** followed by Et_2Zn and then benzaldehyde (Ohno procedure). In the alternate procedure (Walsh), where Et_2Zn and **1a** were premixed, there is linearity. Mechanistic implications are discussed. *To cite this article: Timo O. Luukas et al., C. R. Chimie 5 (2002) 487–491* © 2002 Académie des sciences / Éditions scientifiques et médicales Elsevier SAS

nonlinear effect / asymmetric amplification / asymmetric catalysis / diethylzinc / titanium tetraisopropoxide

Résumé – L'addition d'organozinciques sur des aldéhydes en présence de $\text{Ti}(\text{O}i\text{-Pr})_4$, catalysée par des disulfonamides chirales **1**, est une bonne méthode de synthèse des alcools secondaires ayant des excès énantiomériques élevés. Deux modes opératoires ont été décrits dans la littérature pour préparer le catalyseur. Nous avons réexaminé ces réactions dans le cas d'une catalyse par le (1*R*,2*R*)-bis(trifluorométhanesulfonamido)-cyclohexane **1a**. Le mode opératoire **A** selon Ohno consiste à mélanger $\text{Ti}(\text{O}i\text{-Pr})_4$ et **1**, puis à ajouter Et_2Zn , suivi du benzaldéhyde. Le mode opératoire plus récent de Walsh utilise le mélange préalable de Et_2Zn et **1**, suivi de l'addition séquentielle de $\text{Ti}(\text{O}i\text{-Pr})_4$ et du benzaldéhyde. En utilisant **1a** avec des excès énantiomériques variés, on constate un effet non linéaire positif (amplification asymétrique dans la méthode **A**), tandis que la méthode **B** conduit à une relation linéaire entre les excès énantiomériques de l'alcool **2** produit et de l'auxiliaire chiral **1a** employé. Les implications mécanistiques de ces observations sont discutées. *Pour citer cet article : Timo O. Luukas et al., C. R. Chimie 5 (2002) 487–491* © 2002 Académie des sciences / Éditions scientifiques et médicales Elsevier SAS

effet non linéaire / amplification asymétrique / catalyse asymétrique / diéthylzinc / tétra-isopropoxyde de titane

1. Introduction

The asymmetric addition of dialkylzinc reagents to aldehydes is a widely used carbon–carbon bond forming reaction. A great variety of catalysts provided a high enantioselectivity [1]. β -Aminoalcohols were initially selected as chiral catalysts; they gave rise to the most extensive studies of nonlinear effects (NLEs)

[2–4]. Titanium complexes, which employ chiral bis(sulfonamide)- [5–9] or diols- [10, 11] based ligand systems were subsequently used and are currently the most popular catalysts [12].

Two different methods have been proposed to perform the alkylation of aldehydes catalysed by bis(sulfonamides) **1** (Fig. 1) or analogues in the presence of titanium isopropoxide (in stoichiometric or sub-

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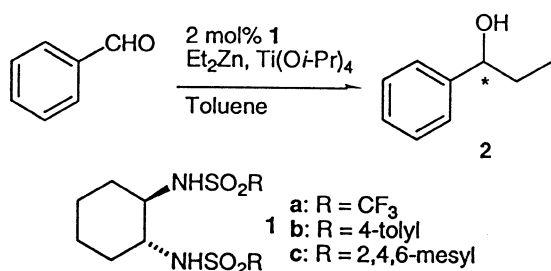


Fig. 1. Alkylation of benzaldehyde.

stoichiometric amount with respect to aldehyde). Ohno et al. first mixed **1** and Ti(O*i*-Pr)₄ at 40 °C for 20 min, and then added Et₂Zn at –78 °C and benzaldehyde (method **A**) [5, 6].

Walsh et al. reported later an alternate preparation of the catalyst (method **B**), where diethylzinc and the ligand **1** were first combined in toluene at 23 °C, ethane was evolved [7–9]. After cooling at –50 °C, a hexane solution of Ti(O*i*-Pr)₄ was added, followed by benzaldehyde and the reaction mixture was allowed to warm to –25 °C.

We reinvestigated these reactions, by varying the enantiomeric excess of the catalyst **1a**.

2. Results

The difference between protocols **A** and **B** that we used may be summarised as follows:

A: Ti(O*i*-Pr)₄ + **1** then Et₂Zn then PhCHO

B: Et₂Zn + **1** then Ti(O*i*-Pr)₄ then PhCHO

Walsh et al. have explored the possibility of aggregation of the catalyst under the reaction conditions (method **B**), by performing nonlinear studies. They found a linear correlation between the ee of the product and the ee of the auxiliary [8, 9]. They also succeeded to get crystal structures of titanium complexes of **1b** and **1c**, the titanium was observed to be bound to one oxygen of each sulfonamido group [8]. Walsh et al. also prepared and studied the structure of complexes bis-(sulfonamido)Ti(NMe₂)₂. The bis(sulfonamido) ligand was found to be bound to the titanium through two sulfonyl oxygens in addition to the two sulfonamido groups [13].

To investigate a possible nonlinear behaviour in asymmetric catalysis of various bis-sulfonamides, we performed a series of reactions with the original Ohno procedure (method **A** [5, 6]). We detail here the exact protocol that we used. Bistrifluorosulfonamide **1a** (2% mol equiv) and titanium isopropoxide (1.2 equiv), which was diluted in hexane, were added at 23 °C in toluene, and then heated for 20 min at 40 °C to solubilise the reactants. After cooling at –78 °C, diethylzinc

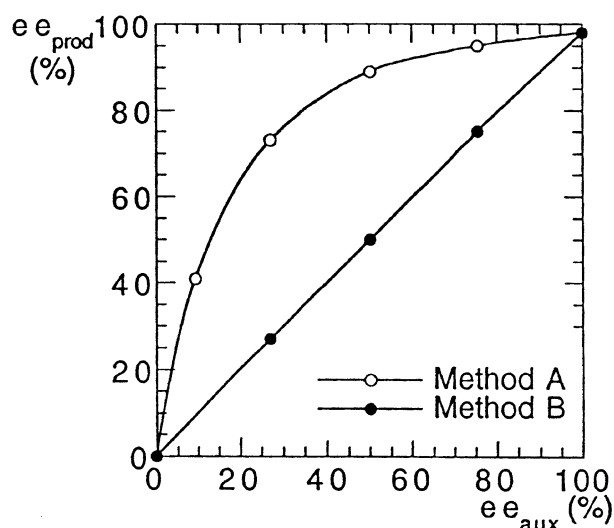


Fig. 2. NLEs of catalyst prepared by two different methods, in the reaction of Fig. 1.

inc (1.2 equiv) was added, followed by addition of 1 equiv of benzaldehyde, and the temperature was raised to –24 °C. We were surprised to find a strong (+)-NLE (e.g., asymmetric amplification). We performed another set of reactions to compare with Walsh's results (method **B**) using his experimental conditions (catalytic loadings, reactants, solvents, scale etc) [7]. We observed linearity between the ee of the ligand and the ee of the product, in excellent agreement with the report of Walsh et al. [8, 9]. Fig. 2 displays the results that we obtained with method **A** (Ohno procedure [5]) and method **B** (Walsh procedure [7–9]), using bistrifluorosulfonamide **1a** as catalyst precursor.

2.1. Method A

In a flame-dried Schlenk was placed ligand (0.05 mmol) under argon atmosphere. To this was added degassed toluene (1 ml) and Ti(O*i*-Pr)₄ (3 mmol), and the mixture was stirred at 40 °C for 20 min. After being cooled to –78 °C, Et₂Zn (1.0 M, 3 ml, 3 mmol) was added to the solution. In a moment, the solution turned orange. To the resulting solution was added benzaldehyde (2.5 mmol) in toluene (0.2 ml) and the mixture was warmed to –24 °C, and was let to react at this temperature for 18 h. The reaction was quenched by adding 1 M HCl, and the product was extracted with diethyl ether. The solvent was removed by evaporation under reduced pressure. The residue was distilled under reduced pressure (95 °C/10 mm Hg), giving pure 1-phenyl-1-propanol [5]. Enantiomeric excess was determined by HPLC analysis using Chiralcel OD-H column, and a 98:2 mixture of *n*-hexane and *i*-PrOH as eluent.

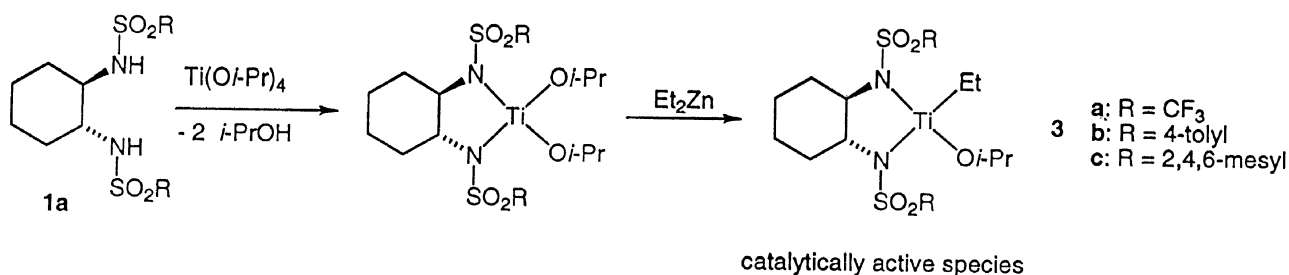


Fig. 3. Mechanistic assumption for alkylation of aldehydes by Et₂Zn as initially proposed by Ohno et al. [6].

2.2. Method B

In a flame-dried Schlenk were placed ligand (0.05 mmol) and diethylzinc (1.2 equiv), which were combined with 3 ml of toluene under argon atmosphere. The Schlenk was cooled to $-78\text{ }^{\circ}\text{C}$ instead of $-30\text{ }^{\circ}\text{C}$ in [7]. Ti(O*i*-Pr)₄ (1.2 equiv) in hexane (1.5 ml) was added slowly by syringe. Upon addition of titanium tetraisopropoxide the solution became orange. The solution was stirred for 5 min and benzaldehyde was added (1 equiv). The resulting solution was checked for homogeneity, transferred to a $-24\text{ }^{\circ}\text{C}$ bath, and stirred for 18 h. The reaction was quenched with 1 M HCl, and the product was extracted with diethylether. The solvent was removed by evaporation under reduced pressure. The residue was distilled under reduced pressure ($95\text{ }^{\circ}\text{C}/10\text{ mm Hg}$), giving pure 1-phenyl-1-propanol. Enantiomeric excess was determined by HPLC analysis (see above).

2.3. Discussion

Clearly, the asymmetric amplification is due to the catalyst preparation procedure. Does the inverse addition in the formation of the catalyst in method **B** give rise to a different catalytic species? We shall discuss our results in the light of the mechanistic assumption of the literature. Ohno et al. proposed for method **A** the mechanism described in Fig. 3. Walsh et al. [8] have shown that no reaction occurs by mixing **1** with Ti(O*i*-Pr)₄, while Denmark et al. [14] established that addition of diethylzinc to sulfonamides such as **1** forms some strongly self-associated species **4**, as indicated in Fig. 4. For these reasons, Walsh et al. suggested an alternative mechanism to the mechanism of Fig. 3 of Ohno et al. and proposed the initial formation of **4** (Fig. 4), with further transformation into the monomeric and catalytically active titanium species **3**.

It remains unclear if it is the reversal of the order of mixing from **1**, Ti(O*i*-Pr)₄ and Et₂Zn (method **A**, Ohno procedure) to Et₂Zn, **1** and Ti(O*i*-Pr)₄ (method **B**, Walsh procedure) which changes the structure of the actual catalytic species. Another possibility could be the different temperatures used in methods **A** and

B to prepare the catalyst. Obviously, some difference must exist between the two methods, as reflected by the strong (+)-NLE occurring only for method **A**. What could be this difference?

In order to answer to this question we performed some kinetic studies on the both systems (Fig. 5). The reaction rate with method **A** was much slower if the ee of the auxiliary was small (compared to the enantiopure catalyst). In method **B** the reaction rate was not affected by ee_{aux}.

The slowdown of the rate in method **A** for decreasing ee_{aux} fits with the presence of a (+)-NLE. It is well documented that asymmetric amplification is

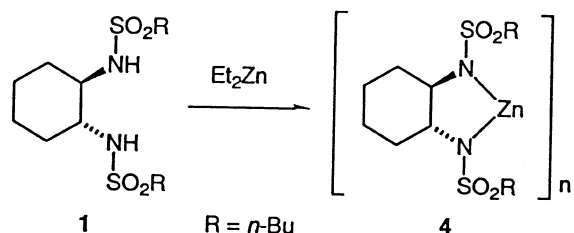


Fig. 4. Addition of diethylzinc to sulfonamide **1**.

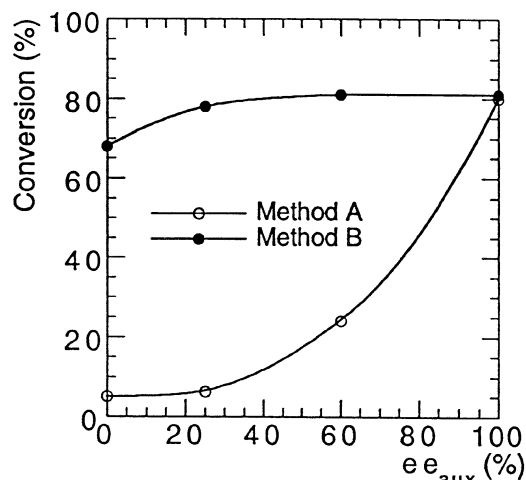


Fig. 5. Rates of reaction (yield) with catalysts prepared by method **A** (●) or **B** (○).

associated with decreasing rates for low ee_{aux} , which is in agreement either with the ML_n kinetic model [15, 16] or with the reservoir effect [4]. We recall that the reservoir has been defined by the formation of diastereomeric species external to the catalytic cycle, usually of racemic composition, while, in the kinetic model, a heterochiral catalyst less active than the homochiral catalyst is at the origin of the asymmetric amplification [17]. We studied the influence of the temperature (and of the heating time) on the (+)-NLE in method A. As shown in Fig. 6, there is a clear beneficial effect by increasing temperature and time of the catalyst preparation. It could be related to the enhanced production of a ‘reservoir’ product of racemic composition, whose formation is slow at room temperature. The most simple hypothetical structure could be a dimeric titanium complex (5, Fig. 7), although higher molecular-weight polymers are also possible. With this hypothesis, there should be no difference between enantiopure catalysts prepared by methods A or B. As a test, we investigated the addition of diethylzinc on racemic hydratropaldehyde in the presence of catalyst A or B. The isolation procedure of products and the chromatographic analysis were carried out according to [18]. We found an absence of kinetic resolution in the two experiments. Moreover, both reactions proceeded at identical reaction rates with enantiopure catalysts A and B.

It must be noticed that $Ti(Oi\text{-}Pr)_4$ was used in stoichiometric amounts by respect to aldehydes, e.g., in large excess by respect to the sulfonamide ligand [5–9]. However, it has been observed that a large excess of titanium complex is unnecessary for achieving good ees and yields [6]. We found, for example, that a decrease of the proportion of titanium in $Ti(Oi\text{-}Pr)_4/1a/PhCHO$ from 1.1:0.01:1 (methods A and B) to 0.1:0.01:1 and then to 0.04:0.01:1 leads to **2** with 98% ee , 84% ee and 33% ee respectively, the yields remaining good. Stoichiometric amount of titanium catalyst is needed for achieving high ee , although sometimes some titanium complex is involved as catalyst and not as reagent. Seebach et al. [19] have shown that a spirotitanate derived from Taddol and $Ti(Oi\text{-}Pr)_4$ is a good enantioselective catalyst for the addition of diethylzinc on aldehydes. It gives a strong

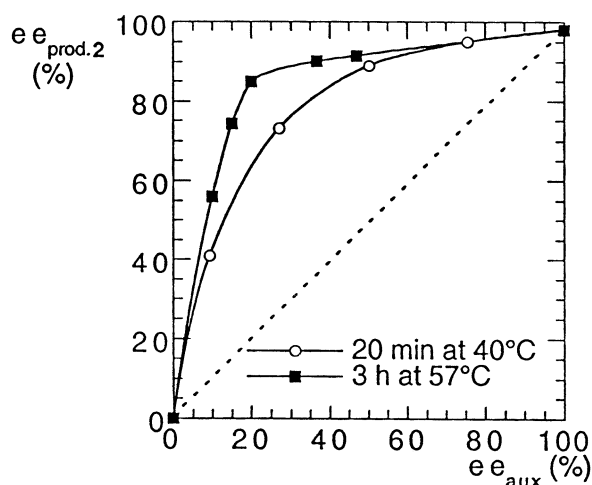


Fig. 6. Method A. Influence of the temperature and time in the catalyst preparation before addition of Et_2Zn .

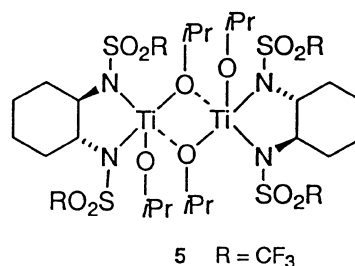


Fig. 7. Dimeric titanium complex 5.

acceleration of the reaction with respect to $Ti(Oi\text{-}Pr)_4$ used in catalytic amounts. The absence of NLE is in agreement with a monomeric structure for the catalyst.

We are currently investigating the mechanistic details of this catalyst, which remains the favoured one for the enantioselective addition of organozincs on aldehydes [12], because of its robustness and the ease to get the two enantiomers of **1**. It was recently shown that the *meso* analog of **1** combined to a tetra-alkoxide titanium complex derived from $Ti(Oi\text{-}Pr)_4$ and (*S*)- $PhCH(Me)OH$ led to an enantioselective catalyst, an evidence for the importance of both the alkoxide and sulfonamide ligands around titanium [20, 21].

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